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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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SURGERY

VOL. 40 OCTOBER, 1956 No. 4

Original Communications

THE RESISTANCE TO CANCER

JOHN J. MORTON, M.D., ROCHESTER, N. Y.

(From the Department of Surgery, The University of Rochester School of Medicine and Dentistry)

THE physician who follows his cancer patients through the years will be impressed by the different types of reaction to the disease. Some cancers will have a rapid evolution and will progress without any evidence of a delaying response by the body tissues. Others will be relatively slow in their progress taking a number of years for full extension. In a third group, the body tissues will exhibit undoubted resistance to the growth of the cancer rendering it incapable of spread and even, in some instances, causing it to disappear. Every surgeon of experience will have had some remarkable cases of cancer in which the patient lives for years with cancer still present. As of today it is difficult to account for these chronic cancer patients. In this group there will be those patients who show much longer survival than is average for a particular type of cancer, and those who show spontaneous disappearance either of the primary tumor or of secondary implants. There will be patients with cancers that grow in cycles with periods of rapid growth alternating with stationary periods or actual regressions, patients in whom delayed recurrence appears in the scar of the previous operation or in its immediate neighborhood, patients in whom the cells have remained dormant in organs, lymph nodes, or in tissues without producing symptoms, and similar patients in whom the cancers regain their vigor at a later time and have a rapid spread throughout the body.

In 1953, we assembled 17 cases of cancers of the chronic type from our own clinical material. We culled from the literature 43 cases, other than ours, of breast cancer with recurrence or metastasis ten years or more (up to fifty years) following operation. We found 25 cases, other than ours, of malignant melanoma with recurrence or metastasis from six years to twenty-

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two years after operation. Instances of a chronic course for malignancies of the thyroid, stomach, intestine, lung, salivary glands, kidney, adrenal, uterus, ovary, testis, bone, fibrous tissues and of the leukemias are recorded in the medical literature.[64]

A few examples of this type of response to cancer will be given now.

There is without doubt a resistance to cancer in some individuals and probably also an increased susceptibility in others. Have we any scientific evidence for either resistance or susceptibility from animal experimentation? Can resistance or susceptibility be induced? What is the nature of such responses? Is there any hope that resistance to cancer can be produced in humans?

The Transplanted Tumor.—Experimental cancer studies became possible when it was shown that tumors of rats and mice could be transplanted into other rats and mice. This whole field was intensively studied and much was learned about the laws governing successful growth of tumors. The transplanted tumor was in essence a tissue graft. The laws of tissue grafting hold for all tissues of the animal kingdom, whether normal or neoplastic. It was learned early that autografting, the transfer of one's own tissues, was the most successful; that homografting, the transfer of tissues to the same species was much less successful; and that heterografting, the transfer of tissues to other species, was never successful except under certain modifying conditions.

The autograft: Autografting of tumors is demonstrated by metastatic growths. This is the feature that makes malignant tumors the difficult problem that they are. There is evidence that not all cancer cells which get into the lymphatic or blood stream survive. In this regard they behave in a manner not essentially different from that of bacteria introduced into the blood stream. It has been repeatedly demonstrated that bacteria under such conditions are handled by the body's defense mechanisms—agglutination in certain organs (liver, spleen, lung) and phagocytosis in these organs by histiocytes, macrophages, and other cells. The dosage must be massive and repeated before the natural resistance is broken down. This is one basis for removing the infecting focus, or the primary tumor.

Tissues which may be successfully autografted are skin, connective tissue, cartilage, bone, fat, blood, blood vessels, nerves, and possibly thyroid, parathyroid, and adrenal glands. The success or failure of the autograft varies with the species, and with many other factors.

Skin autografts survive with their appendages: hair, glands, pigmented spots, angiomas, and dermal portions not only in covering favorable skin defects but also retain their structures over bone and mucous membranes in unlike areas.

Connective tissue as fascial autograft usually survives as fascia. Tendon with the sheath as autograft survives as tendon and matrix when in contact with tendon.

Cartilage as autografts from rib, nasal septum and ear appears to survive with viable chondrocytes. New cartilage formation does not occur but new bone and connective tissue may partially replace it.

Bone as autografts from cancellous portions of rib, tibia, and iliac bone, with or without periosteum, if in contact with living bone shows persistence of osteocytes and callus formation joining the bones. Dense cortical bone as autograft is replaced by "creeping substitution" from the host cells, retaining its form, however.

Fat as an autograft, if very carefully handled, has a portion of its favorably situated cells and its vascular supporting tissues survive.

Blood can be reinfused as necessary when massive hemorrhage has occurred as in the peritoneal or pleural cavity.

Blood vessels used as autografts retain their muscle cells and lumen but the fate of the intima is not resolved. The host intimal cells may quickly overgrow and replace the graft intima.

Nerves as autografts survive only in the sheath cells but serve as bridges across which the new axones may grow.[68]

Several years ago successful reimplantations of removed parathyroid, thyroid, and adrenal tissues were reported. These experiments have not led to observations of a similar nature which seems to indicate that the success was not striking enough to stimulate additional efforts.[77]

The homograft: The success of homografting depends upon hereditary constitution, tissue compatibility, and early accommodation of the graft to its nutrition.

The only homografts of skin which survive permanently in the human being are those from single ovum (identical) twins (in reality these are isografts; grafts between individuals of the same genotype) and grafts to hosts which cannot manufacture gamma globulin.[83]

In homocorneal grafts the surface epithelium is replaced by the host cells. Some reporters believe that the cells in the deeper connective tissue layers tend to survive and retain the clear structure; others believe all the cells are replaced by those of the host.[52, 54]

All the living cells in fresh or preserved fascial homografts die. The graft is invaded by host blood vessels and host fibroblasts. The fate of the graft collagenous fiber matrix is not known.

Homografted tendon cells do not remain viable long; the collagenous fiber matrix persists longer but is ultimately replaced by host fibroblasts.

Homografts of cartilage retain their shape and the chondrocytes survive as long as the protection of the matrix shields them from the host tissues.[7, 8, 46]

Homografts of fresh or preserved bone, cancellous or cortical, is gradually replaced by "creeping substitution" of tissues from the host.

Homografts of blood vessels, fresh or preserved, are destroyed by the reaction of the host within three weeks with the exception of the elastic tissue which persists.[78]

Homografts of blood are successful in transfusions when the groups consist of compatible cells and serum.

Homografts of sperm to ova constitute an intracellular graft which is frequently successful.

The only cells of homografts in the human being which survive for long periods of time are possibly some cartilage cells, the connective tissue cells of the cornea, the lens, and certain red blood cells in transfusions.[52, 69]

Homografts of animal tumors are successful when dominant genes are simultaneously present in the graft and in the host and there is very close tissue compatibility, in brother to sister mated strains over long periods, (Little; mice) or pedigreed animals (Rous; chickens).[50, 51, 76]

The heterograft: The heterograft is not viable in the host except under certain modifying conditions. It is invaded by the host tissues and replaced, absorbed, or extruded.

The exceptional modifying conditions are transplantation to the eye,[26] transplantation to the brain,[74, 67, 27] transplantation to the hamster's buccal pouch,[48] the use of x-ray,[66, 15, 80] and the conditioning of the adult tissue by tissue injections into the embryo.[11, 81, 20, 73] These will be discussed later.

CAN RESISTANCE OR SUSCEPTIBILITY BE INDUCED?

Little and his co-workers,[51, 75] working with mouse cancers, found four laws of transplantation which hold for these homografted tumors and probably for all homografted normal tissues as well. These are:

1. Tumor isotransplants (same genotype) within the strain of origin grow progressively and kill all hosts.
2. Tumor homeotransplants (different genotype) within the species but outside the strain of origin fail to grow or grow temporarily and then regress.
3. F_1 hybrids produced by crossing two inbred strains will grow tumors indigenous to either parent strain.
4. Only a fraction of mice of an F_2 generation or a back cross produced by mating the F_1 to the resistant parent, will grow tumors from the inbred lines involved. The portion susceptible may be large or small depending on the tumor and the cross. It rarely exceeds 75 per cent for the F_2 or 50 per cent for the back cross (Snell).[76]

The accepted genetic theory of transplantation is that susceptibility is due to multiple dominant genes. Successful transplantation depends on the presence of dominant genes simultaneously in the graft and in the host (Little; Hauschka).[51, 32] These genes may be called histocompatibility ("tissue") genes. In the mouse there may be six or seven of these genetic loci and probably more (Snell).[75] By the use of "marker genes" it has been possible to detect linkages. Such "marker genes" with visible effects as coat color, fused tail, Gorer's red cell antigen II can be used to identify the gene loci.

When a homeotransplant of a tumor grows and then regresses it confers a resistance to future transplants of the same tumor, *acquired resistance.* In transplanting cancer into a group of animals there will be certain animals which fail to grow the graft. This is an instance of *natural resistance.* It was found that normal tissues of the animal when injected with certain dosages followed by certain elapsed time intervals, conferred resistance to the inoculation of tumor grafts in a high proportion of animals.

Many different techniques have been used to produce the resistant states. The doses and the intervals have varied, and the injection routes; the cells have been frozen, heated, dried, and injured by chemicals before injection. This has resulted in great confusion in establishing principles of resistance.

Certain preparations of cells cause increased resistance to the growth of homotransplanted tumors or normal tissues. Living normal or tumor cells,[89] small doses of lyophilized normal[38, 39] or tumor cells,[75, 76] and some vital stain dyes[79] can confer increased resistance to normal or tumor homotransplants. On the other hand, large doses of lyophilized normal or tumor cells,[38, 39, 75, 76] heated emulsions of tumor cells,[21] frozen material,[47] filtrates of autolyzed[14] or refrigerated tumors,[12] and some vital stain dyes[79] can cause increased susceptibility to transplanted tissues. From this superficial review it is evident that resistance or susceptibility to homografts can be produced in a variety of ways. Dosage of the materials used is critical and increased susceptibility can be brought about as readily as increased resistance. The induced resistance or susceptibility is species-specific and only tissues at the species level or within the species are effective. Thus injection of rat, guinea pig, or hamster tissues will not confer either resistance or susceptibility to mouse tumor transplants.

WHAT IS THE NATURE OF SUCH RESPONSE?

The increased resistance to transplantation of either normal or neoplastic tissue is an antigen-antibody phenomenon. The increased susceptibility to transplantation of tumor tissue is the resultant of breaking down the antibody defense.

There is ample evidence from studies on skin homografts that a large first graft immunizes more effectively than small ones; and that a second skin homograft will slough more rapidly than the first one (Medawar).[56] The graft appears to be viable for a period of time, sometimes up to several weeks, but then it disappears. This latent period is necessary for the development of antibodies to the skin which acts as the antigen. If a second graft is applied the latent period is much less–"the secondary response." The intensity of the antibody formation varies directly with the length of the period over which the antibody-forming cells have been subjected to the antigenic stimulus. As many antibodies are formed as there are antigens to stimulate their formation (Medawar).[57, 58]

Most substances that are fully antigenic are proteins. But substances simpler than proteins may have antigenic activity by virtue of their linkage to proteins, i.e., polysaccharides of the pneumococcus capsule. Many of the polysaccharides are partial antigens or haptens. They carry the specific reacting group. Antibodies are modified globulins and gamma globulins above all else. Properdin, a euglobulin found normally in the blood acts as a nonspecific primordial bactericidal and virucidal agent (Holden).[34] Many attempts to localize the antibody formation have been made. Organs have been destroyed, cells blockaded, and distribution of the antigen studied by extraction of different organs. Tagged lysin has been used by Miller and Bale[61] who showed that gamma globulin formation is widespread in the body in con-

trast to the localized formation of beta globulins and other plasma proteins. Results of many studies suggest that gamma globulin antibodies are formed by the reticuloendothelial system, lymphocytes, and plasma cells.

Following an optimal injection of an antigen there is a lag period of a few days and then the appearance in the blood of the corresponding antibody. The titer rises rapidly to a maximum which is usually attained between the tenth and twenty-second day after inoculation.

The titer then falls, at first rapidly, then more slowly, until it reaches a level which is maintained for several months.

The final disappearance of antibodies from the blood stream may not occur for many months or even years.

The amount of antibody produced varies with the amount of antigen although the increase in titer is not in simple proportion to the increased antigen dosage. Response to subsequent injections is usually more rapid and more copious than to the initial injection (Topley).[82]

Precipitins, agglutinins, lysins, opsonins, and bacteriotropins do not designate different antibodies but the same antibody doing different things (Topley).[82] Mice form at least four kinds of antibody in response to tumor inoculation: (1) ordinary saline agglutinins, (2) agglutinins active only in high concentration of mouse serum, (3) agglutinins inactive in mouse serum but active in human serum, (4) an agglutinin active in heated human serum but lysed in unheated human serum (Hauschka).[31]

The progressive growth of a tumor transplant in a foreign host and the successful "take" of a normal tissue homograft is an active phenomenon of competition between the transplant which tries to overflow the host with its antigens and the host which tries to overcome the graft with its specific antibodies. The final result will depend on the relative proportions of both processes. A shift in the antigen-antibody balance would result either in resistance or susceptibility to the graft (Snell).[76]

Studies of the tissues about a failing graft indicate that there is a marked cellular response with accumulation of cells of various types: lymphocytes, leukocytes, plasma cells, reticuloendothelium, histiocytes, macrophages, connective tissue and new blood vessels.

The cells responsible for the resistance process have been thought to be reticuloendothelial cells, lymphocytes, and plasma cells especially, and there is good experimental evidence to support each.[55]

Murphy and Morton[66] were convinced that the lymphoid tissue had a part in the resistance to tissue grafting in a foreign species, and that the natural or induced immunity to transplanted homografted cancers was due to the lymphoid reaction. Chick embryos which had no defense against the cells of a foreign species became as resistant as the adult when supplied with adult lymphoid tissue (spleen). Also, repeated small doses of x-ray given to an adult animal deprived it of its ability to destroy the cells of a foreign species. The previous destruction of the lymphoid tissue with x-ray destroyed the immune state.

Using this method Clemmesen[15] found that tumors could successfully be transplanted to x-rayed heterologous hosts. He thought that the effect of the x-ray was to delay the immune reaction. Once the immunity to a heterologous graft had been acquired, x-ray could not break it down.

Toolan[79] made use of this principle for the transfer of human tumors to irradiated rats, mice, and hamsters. She found that newborn, nursing rats were highly resistant to irradiation effects and were poor hosts to human tumors. But weanling rats, 25 to 35 days of age, following irradiation grew human tumor minces rapidly for fourteen to twenty days before regression. If cortisone was given to the rats in addition the results were even better. The human tumors grew better in the weanling rats than in the human hosts. They could be propagated relatively easily in tissue culture and also on the chick membrane. Rats in which the human tumors had regressed were not made susceptible to other human tumors by second irradiation even though the lymphocyte count was reduced.

Cortisone treatment alters the host's stroma reaction by not allowing sufficient nourishment to get to the grafted tissues in time. This would also delay the antibody response if the cellular reaction was prevented. Cortisone acts as a damper to the inflammatory reaction. Krohn[44] treated rabbits with cortisone and was able to prolong "the second-set" skin graft survival appreciably.

Mitchinson[62] has shown that immunity to mouse lymphosarcoma can be passively transferred through lymph nodes implanted from a previously immunized strain to the same strain not so treated. Serum was not effective but the lymph-node cells were. The lymph nodes in the immunized strain doubled their normal weight. In additional experiments he has shown that cells from the lymph nodes draining a tumor homograft transferred as a mince into the subcutaneous tissues, or as a suspension into the peritoneal cavity, could confer immunity to the secondary host. These cells could confer immunity while the immunizing graft was undergoing breakdown and especially during "the secondary response." Cells from other lymph nodes not draining the tumor, spleen, whole blood, and the serum failed to transfer immunity. Freezing and thawing of the transferred cells prevented the transfer of immunity. The antibody effective against the homografts was bound to the cells, presumably lymphocytes.[63]

Kidd and Toolan[43] found that, in tumor-resistant mice, lymphocytes accumulated regularly and in force. They penetrated the cancer cells and broke them down, first peripherally, then centrally. The cancer cells died. Humoral antibodies had no discernible effect in the immune process.

Normal spleens and lymph nodes had no effect, nor did serum from immune rabbits (Ellis and Kidd).[18]

Several investigators have shown that antibody-producing tissue, whether splenic or lymphoid, from immunized animals may continue to produce antibodies in vitro (Mountain).[65]

Medawar,[58] however, was unable to find cytotoxic antibodies to homologous skin in the lymphoid tissues of immunized rabbits.

Working in tissue cultures, Pomerat[70] demonstrated the effect of Reticuloendothelial Immune Serum (REIS) on the growth of rat sarcoma. The cells of this tumor were inhibited by homologous antirat REIS but not by heterologous antichick REIS. Outgrowth of tumor cells was reduced when splenic cells were included in the medium but not in controls containing no REIS. It was suggested that the inhibitory action of the spleen on tumor cells was exerted in the presence of relatively strong concentrations of REIS. In eggs, the injected spleen may cause the developing embryo to produce the necessary REIS.

Algire,[2] using the transparent chamber technique, has demonstrated that the graft from a growing tissue is not passive. It plays an active role in its own initial vascularization. Very frequently there is an outgrowth of endothelial sprouts from the blood vessels of the graft and it may re-establish its circulation with its original blood supply in less than twenty-four hours.

Merwin and Hill,[59] found that homografts of thyroid or Harderian glands of newborn mice in Algire's chamber technique are destroyed if they become vascularized but survive indefinitely in the subcutaneous site as long as they remain nonvascularized.

Algire, Weaver, and Prehn[3] undertook to prove whether the resistant state was due to humoral or cellular elements, or both. They constructed diffusion chambers with filters which either excluded or admitted host cells. They showed that homografts of Harderian gland or mammary adenocarcinoma survived in the chambers of previously immunized resistant mice indefinitely if the host cells were excluded. They concluded that both the antigen and the mobile resistant factor in some types of homograft immunity existed to a critical extent in intimate association with cells rather than in a free or humoral state.[71] In their latest reported experiments it was demonstrated that the "immunized" cells which were responsible for the death of the target cells were lymphocytes. When these lymphocytes contacted cells to which they had been "immunized" both types of cells died. Such death was followed by release of diffusible substances (antibodies and antigens) which killed near-by cells of both types. They made a strong case for the lymphocyte as the responsible cell which transported the antibodies to the homografts.[86]

Most immunologists follow Fagraeus,[19] who believes that there is no direct evidence for antibody formation in the reticuloendothelial system; that the lymphocyte antibody formation is for animal experiments only and not for human pathology; and that the weight of evidence both from animal experimentation and human pathology supports the plasma cell as the site for antibody formation.

The majority of hematologists think that the plasma cells originate from the reticulum cells and not from lymphocytes. The formation of antibodies takes place side by side with, and during the development of reticulum cells into plasma cells. Antibodies are formed within the reticuloendothelial cells. In case of an intense antibody formation, a differentiation of reticuloendothelial cells into plasma cells takes place.

There is without doubt both a cellular and a serological response in the immunized animal.

It is not always possible to demonstrate antibodies of any kind when a tissue graft is undergoing regression. Occasionally antibodies can be demonstrated and the grafted tumor continues to grow, this is presumably due to a low titer. Precipitins, complement fixing, and lymphocytopenia-producing antibodies may be demonstrated, but it is by no means certain that they are responsible for the regression of the graft.

Gorer[25] immunized mice against a transplantable leukemia. The sera from these mice contained a protective antibody against the leukemic cells. There was also a hemagglutinin which could be separated from the protective antibody by absorption.

Amos, Gorer and associates[5] found that incompatible skin homografts in mice stimulate the formation of antibodies that react with red blood cells and leukocytes. Hemagglutinins may be present in mice, and if so they are susceptible to tissue transplantation. Resistant mice lack this hemagglutinin antigen, a situation similar to Rh sensitization in the human.

Precipitins and cytotoxins to human skin were produced by immunizing rabbits with human skin suspensions. When normal homologous rabbit skin was used as antigen, no precipitins or cytoxins to human skin were produced. Normal homologous or heterologous serum does not contain demonstrable antibody to the foreign epithelium, nor does immunized homologous serum, but immunized heterologous serum does. It takes the coarse contrast between species, potentiated by the immune response, to show the antibodies (Allgöwer and associates).[4]

Cytotoxins in tissue culture indicate that the proper conditioning tissues must be present to give the effects. For instance, mouse and rat cells in vivo give a marked immune response; in vitro, they will grow side by side without producing any immune response. The serum of normal rats gives no effect on mouse cancer cells in vitro; but the serum of rats immunized against mouse cancer cells not only has lethal effects on mouse cancer cells in vitro, but also on other mouse tumors and on normal mouse cells. There will be no effect on cancers of different species, or on cultures of normal rat cells, or on cultures of cells of other foreign species. The cytotoxins involved are *anti-species* antibodies (Harris).[29, 30]

The resistant state can be influenced or conditioned by various means so that it is not effective. In most instances, this is accomplished by retarding or overcoming the antibody response. Sometimes it is done by changing the tissues before the antibody response develops. It is known that human red blood cell antibodies are absent, or almost so, at birth. Whatever agglutinins are present appear to be derived from the mother by passage through the placenta and they disappear by the tenth day of life. These agglutinins gradually increase in concentration with age and reach a maximum about puberty (Irwin).[36]

Billingham and his associates[11] claim that mice and chickens never develop, or develop only to a limited degree, the power to act immunologically

against foreign homologous tissue with which they had been inoculated in fetal life. Animals so treated were tolerant not only of the foreign cells of the original inoculum, but also of skin grafts freshly transplanted in adult life from the original donor.

Newborn mice are, in general, too old for a tissue inoculum to confer tolerance and too young for it to confer immunity.

Toolan[81] injected rat embryos in utero with human skin, thyroid, submaxillary gland, muscle, kidney, and tumor. When inoculated, none of them grew human tumor after birth (four to five weeks old). Rats were not made tolerant to human cells by this intrauterine treatment.

These divergent results might be explained by the time differences of inoculation of the embryos and of the newborn, and by the species differences. If there is too great a delay before the embryo is injected, subsequent specific intolerance to homografting tends to develop.

Felton and his co-workers[20] found that young mice and fetuses of mice injected with specific pneumococcus polysaccharide were unable to make antibodies to this single type of bacterial carbohydrate in later life. This "immunologic paralysis" was explained by Kaplan and his associates,[40] using fluorescent labelled antigens, as a neutralization of the antibody as fast as it formed.

Ungulates like sheep and cattle receive no antibodies from the maternal blood stream during gestation. They get them from the first milk (colostrum) at birth and the wall of the small intestine remains permeable to protein for a matter of hours. The fetus receives no gamma globulin until after birth and is incapable of making its own. Making use of this, Schinkel and Ferguson[73] studied skin homografts in fetal lambs. The grafts were placed in the lambs from the eightieth to the one hundred and seventeenth day of gestation (gestation period of sheep is 150 days). Autografts all survived and grew wool. Nothing remained of any homografts at birth except a small scar. Early fetal necropsy specimens revealed a violent homograft reaction with massive lymphocytic infiltration and vascular breakdown, "all very much the usual thing." The reaction was clearly in progress as early as the ninth day after transplantation, virtually complete at the fifteenth day and complete at the twenty-first day.

Transplantation of tissue grafts and tumors to the eye or to the brain are possible because the tissue spaces of the eye and brain are low in globulins and in cells of the reticuloendothelial system. This is in contrast to the large numbers of lymphocytes present in the dermis. Unless an inflammation induces diapedesis of plasma proteins and cells in the neighborhood of the grafts in the eye or brain, an effective reaction is not possible.

According to Baesick and others,[7, 8] the cornea derives its main nutrition by diffusion from the margin. They have found numerous mast cells around the capillary loops at the limbus. The mast cells are responsible for the production and maintenance of heparin, a mucoitin polysulphuric acid. They believe that the mast cells facilitate the diffusion and nutrition by maintaining a high heparin concentration.

The host tissues and the grafted tissues may be altered so that a different response is possible by many other methods. Endocrine imbalances, cross breeding experiments, foster nursing, and growth substances, all have been used to modify the graft and the soil into which it is planted.

Decision was made not to discuss these altered conditions as it would tend to confuse an already complicated picture. Many of the methods, also, could not be transferred into practical applications for inducing resistance toward human cancer.

Specific hypersensitiveness may develop in the course of natural or experimental bacterial infection. Allergy is characterized by an accelerated and exaggerated reaction to contact with the infecting bacteria or its products. It partakes of the character of immunity in that the allergic reaction is often associated with the localization of infection. It is probably an important factor in the development of natural or artificial immunity (Topley).[82]

Neither induced resistance nor hypersensitivity have so far given any indication of tumor-specific antigens (Hauschka).[31]

IS THERE ANY HOPE THAT RESISTANCE TO CANCER CAN BE PRODUCED IN HUMAN BEINGS?

The Spontaneous Tumor.—

The spontaneously arising cancer in an animal is a different problem from the transplanted cancer. Human cancer is of this spontaneous variety. Many investigators believe that there is very little likelihood of producing a resistant state for human cancer.

Hauschka,[31] after a critical review of the immunologic aspects of cancer concluded, "Eventual demonstration of specific neoplastic antigens appears dubious since the critical results to date have been largely negative." Eichwald[17] stated "Immuno therapy of cancer has been the aim of many investigators, and there are a few who still hold out for it." This writer then encourages the few to still try on the hope that some and maybe all cancers may be caused by infectious or viral agents.

Goldfeder[24] attenuated the tumors of highly inbred mouse and rat strains by critical dosage x-ray treatment. She was unable to render the animals immune to subsequent grafts. The irradiation did not alter the genetic make-up so as to render the tumors antigenic toward the host from which they originally arose. "The possibility of immunizing the host against its own tumor is very questionable."

Barrett[9] made a careful study of the induction of resistance to transplantable mouse tumors. He could not induce any sign of resistance in an inbred strain against a tumor derived from the same strain. He concluded that, "The search for a means of treating human cancer on these principles (autoplastic grafting, sensitizing injections) is likely to prove a fruitless one."

The difficulty revolves about the question as to whether one's own tissues can be antigenic. Formerly it was believed that this was impossible except for the lens which was a special case (Hektoen).[33]

Now it is well known that the human red blood cells produce antibodies. When the Rh factor is present in the developing fetus and absent in the mother, she may become immunized against the cells of the fetus. The resulting antibodies may act on the cells of the fetus producing erythroblastosis fetalis. There has been found likewise a secretor gene (S) which produces either A or B substances in tissue secretions depending upon which one is present in the blood cells and organs. (Wiener: *Blood Groups and Transfusion.*)[88]

Metalnikoff[60] found that injecting the sperm of a guinea pig subcutaneously or intraperitoneally into other guinea pigs resulted in a feeble toxicity, not only for the sperm of the inoculated guinea pigs, but also for the sperm of the donor guinea pig as well. This was an autotoxin. It could be greatly increased after the second and third injections. Male and female guinea pigs produced it equally. Many trials were unsuccessful in producing an anti-autotoxin.

It has been found that auto-antibodies to the kidney can be produced by immunization of animals with mixtures of group A streptococci and kidney of the same species. The streptococci thereby confer antigenicity on renal material which as such is nonantigenic in the homologous species. The auto-antibodies thus formed react with the plain homologous kidney as demonstrated by the collodion particle technique. Auto-antibodies to heart, skeletal muscle, and connective tissue can be produced in a similar manner. Auto-antibodies to human heart were demonstrated in 75 per cent of patients with acute rheumatic fever. The titers ran between 1:40 and 1:320. The antibodies were present during the early and most active stages of the disease and disappeared when the rheumatic process became inactive (Cavelti).[13]

Auto-antibodies to the kidney in human glomerulonephritis could be demonstrated in a high percentage of nephritics at all stages of the disease (Lang and associates).[45]

Innes[35] produced experimental allergic encephalitis by injecting rabbits with whole rabbit spinal cord, together with tubercle bacilli and mineral oil.

Waksman and Adams[84] used sciatic nerve or spinal ganglia with tubercle bacilli as antigen in rabbits. An experimental allergic neuritis was produced. Lesions were seen in the nerve roots, spinal ganglia, and peripheral nerves. The disease came on fourteen days after onset, reached a maximum within three days, remained stationary three to four days and then regressed usually. It bore a strong resemblance to the Guillain-Barré syndrome.

In the experimental cancer field, MacDowell and associates[53] were able to immunize mice naturally susceptible to a transplanted leukemia by dilution of the dose of cells necessary to produce the leukemia. When a very dilute dose was given, all the mice survived and were then able to tolerate the standard leukemia producing 80,000 cells without harm.

Gross[28] caused intradermal sarcomas (induced by methylcholanthrene in the same line of C_3H mice) to regress by injecting diluted doses of a 20 per cent suspension of the sarcoma cells into the skin. But spontaneous cancer indigenous to the strain arose in some of the animals whose sarcoma regressed.

Kidd and Friedewald[41] found a natural tissue antibody regularly present in saline extracts of many normal tissues of rabbits. They found antibodies different from this normal one in the blood of rabbits carrying four transplanted cancers.[22] Kidd[42] found that one of these antibodies was capable of suppressing the growth of Brown-Pearce cancer cells under a variety of experimental conditions.

Aptekman, Lewis, and King,[6] produced a high percentage of immunity in albino rats to tumors native to their strain. Their method was to inject an alcoholic concentrate of the tumor into the transplanted tumors, daily or every other day. A high percentage of the tumors were destroyed and the animals proved immune to subsequent grafts.

Lewis and Aptekman[49] also strangulated transplanted rat tumors by rubber bands so that atrophy occurred. All hosts were then immune to reinoculation of the same tumor.

Weiss[87] demonstrated the self-regulation of organ growth by its own products in tissue culture experiments. Protoplasm synthesis of a given organ yields a template for further reproduction of the organ and diffusible compounds capable of inactivating the former. When the diffusible compounds reach a critical concentration in the humoral pool, growth ceases. Partial removal of an organ will automatically call for compensatory growth.

If we could control the invasiveness of cancer cells and the metastasis the problem would be relatively simple. Coman[16] has made studies on these points. The invasiveness is due to the amoeboid movements of the cancer cells. There is also a loss of adhesiveness associated with a deficiency of local calcium at the cell surface. This allows the cancer cells to detach themselves and wander into the tissue spaces, following the lines of least resistance. The lymphatics offer preformed paths, also capillaries and veins which the cancer cells have little difficulty in penetrating. The tough-walled arteries are rarely penetrated. Once in the blood stream the cells are swept by the current for considerable distances.

The mortality of these embolic cells is very high. Only a small percentage survive when introduced experimentally (Warren and Gates).[85] The number of the embolic cells and the age of the tumor is important. The older it is the more the number of embolic cells. The three commonest sites of metastasis in man are the lungs, liver, and bones of the axial skeleton and trunk. This is as to be expected on the basis of veins of the body. The vertebral veins serve as a channel for bone metastases (Batson);[10] also there are arteriovenous shunts in the lungs, liver, and spleen which allow passage of cells through these organs (Prinzmetal and associates).[72] The growth of embolic cells depends upon the number of cells which reach the capillaries of a given organ. The spleen, muscles, and thyroid, which seem to be poor soil for metastases, will grow tumor equal to those of the more favored site if the cells are introduced into their capillary beds. The lungs apparently afford relatively adverse conditions for tumor growth but they receive many more emboli than other organs do.[16]

Even when there appears to be an immunity there may not be complete sterilization of the tissues. Cells may be caught in the liver, spleen, and elsewhere and some of them may remain alive there, but relatively inactive, for considerable periods.

A change in environment, perhaps in hormone balance, may arouse the dormant cells as in Gardner's experiment.[23]

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FAT EMBOLISM

I. The Amount of Fat in Human Long Bones

Leonard F. Peltier, M.D., Ph.D., Minneapolis, Minn.

(From the Department of Surgery, Division of Orthopedic Surgery, University Hospitals, University of Minnesota)

IS THERE sufficient fat within a long bone to account for the phenomenon of fat embolism which may accompany a fracture of this bone? If the answer is "no" then the source of the fat emboli accompanying fractures must be in some generalized disturbance of fat transport or metabolism. If the answer is "yes," the fat emboli associated with trauma to bone can stem from the local site of injury. This question has generally been answered in the negative on the basis of the published work of Scriba[6] (1880), and Lehman and Moore[2] (1927) who concluded that the amount of fat contained in the human femur was insufficient to cause clinically evident fat embolism.

We have come to believe that the origin of fat emboli accompanying bone trauma must be the local site of injury for the following reasons:

1. At the local site of injury to the bone, there is rupture of the fat cells and free fat droplets. There is convenient egress from the fracture hematoma into the general circulation. There is an increase in the local tissue pressure about the site injury. These three factors are the essential elements in parenchymatous embolism.[3]

2. Fat emboli do not appear in the general circulation of experimental animals with fractures or in patients undergoing elective operations upon the bone if the site of injury is excluded from the general circulation by a tourniquet applied proximally prior to injury.[4]

3. The degree of fat embolization accompanying fracture of the femur in rabbits is not increased by the presence of a concomitant lipemia.[5] If fat emboli have their origin in a systemic disturbance of fat metabolism or transport, they should be more prominent in those animals with the greatest amount of fat readily available in the general circulation.

How did Scriba,[6] and Lehman and Moore[2] arrive at their conclusions? The former took the femora and two vertebrae from a 34-pound dog, pulverized them and extracted this material with ether. After the ether had evaporated, the residue was weighed as bone fat. A similar extraction was made of one femur and two vertebrae of a rabbit. From this data, it was *calculated* that the adult human femur contained 70 c.c. of fat. Lehman and Moore measured the capacity of the marrow cavities of three dried human femora. These measurements excluded the cancellous portions of the bone. Measured sections

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of the diaphyses of two freshly amputated human femurs were heated and the melted fat collected and measured. From this data, and with an expressed desire to approximate the figure given by Scriba, they *calculated* that the fat content of the marrow cavity of an adult human femur was 65 c.c.

Because of the nature of these previous investigations, based on material from one dog, one rabbit, and portions of five human femora, it was decided to carry out further studies to determine the amount of fat actually contained in human long bones.

PROCEDURE

Fresh human bones were obtained from amputation specimens. Information regarding the source of these limbs is shown in Table I. The bones were cleaned of all soft tissue, weighed, and frozen. They were then sectioned transversely into thin slices. These slices were divided into two portions, the metaphyses and the diaphysis, on the basis of gross examination. The femora were sectioned at the level of the lesser trochanter and the adductor tubercle, dividing them into a diaphyseal and 2 metaphyseal portions. The metaphyseal portion contained most of the cancellous bone; the diaphyseal portion, the cortical bone and marrow contents. These two portions were extracted separately.

TABLE I. INFORMATION REGARDING PATIENTS WHOSE LIMBS WERE USED

PATIENT NO.	AGE	SEX	DIAGNOSIS
1.	68	F	Arteriosclerotic gangrene
2.	78	M	Fresh fracture femur, old osteomyelitis
3.	78	M	Arteriosclerotic gangrene
4.	67	M	Arteriosclerotic gangrene
5.	83	F	Diabetes, arteriosclerotic gangrene
6.	68	F	Diabetes, arteriosclerotic gangrene
7.	75	M	Diabetes, arteriosclerotic gangrene
8.	69	M	Diabetes, arteriosclerotic gangrene
9.	88	M	Diabetes, arteriosclerotic gangrene
10.	85	M	Arteriosclerosis
11.	18	M	Osteogenic sarcoma femur
12.	18	M	Osteogenic sarcoma ilium
13.	65	F	Osteogenic sarcoma ilium

The fat was extracted from the bone using 95 per cent alcohol and petroleum ether according to the method of Bloor.[1] The bone slices were dropped into a Waring blender containing alcohol, and morcellated. The mixture was filtered. The residue was extracted with hot alcohol in a percolator. The filtrate and the extract were combined and the alcohol distilled off in a partial vacuum at 60° C. The residue was taken up with petroleum ether. This ether extract was evaporated to dryness. The residue was weighed as bone fat. The results of this procedure are shown in Tables II and III.

DISCUSSION

The data contained in Tables II and III emphasize the considerable variation between individuals. This variation is a function of the size of the bone and its mineral content. While the size of a bone is determined by genetic and dietary factors operating during the growth period, the mineral content of bone fluctuates throughout the lifetime of the individual. Function, with its concomitant stress and strain, increases the mineral content and decreases the fat content. Disuse or nonfunction is associated with atrophy and decrease

in mineral content. The bone fat apparently serves purely as a space-occupying material and, because of its light weight and ready availability as a store of energy, is ideal for this purpose.

The first 10 patients and Patient No. 13 were over 60 years of age, with debilitating disease, and with varying degrees of osteoporosis. Roentgenograms of their bones did not, however, reveal any greater degree of osteoporosis than exists among patients of similar age with traumatic injuries. The amounts of fat reported here are representative of the fat content of the bones in patients of this age group.

Patients No. 11 and No. 12 were both active young men in whom there had been no functional impairment or interference with activity due to their disease. The bones of these individuals were more difficult to cut and to morcellate. There was no atrophy or osteoporosis here. Yet the fat content

TABLE II. THE AMOUNT OF FAT IN HUMAN LONG BONES

		WET WEIGHT OF BONE (GRAMS)			AMOUNT OF EXTRACTED FAT (GRAMS)		
PATIENT	BONE	METAPHYSES	DIAPHYSIS	TOTAL	METAPHYSES	DIAPHYSIS	TOTAL
1.	tibia	121.4	115.1	236.5	47.6	37.4	85.0
2.	tibia	365.5	257.4	622.9	67.8	19.2	87.0
3.	tibia	368.6	248.0	616.6	140.1	49.2	189.3
4.	tibia	195.3	196.7	392.0	41.9	18.5	60.4
5.	tibia	165.3	141.6	306.9	75.3	62.0	137.3
6.	tibia	236.9	212.5	449.4	67.7	35.1	102.8
7.	tibia	261.5	198.0	459.5	—	—	119.5
8.	tibia	238.0	231.0	469.0	73.6	36.6	110.2
9.	tibia	376.2	226.0	602.2	—	—	221.9
10.	tibia	173.9	158.9	332.8	78.7	37.2	115.9
11.	tibia	228.1	240.1	468.2	78.3	42.8	121.0
12.	femur	460.3	408.7	869.0	82.2	39.4	121.6
	tibia	305.4	199.1	504.5	84.7	27.6	112.3
	fibula	—	—	104.6	—	—	12.0
	tarsals	—	—	230.7	—	—	46.8
13.	femur	318.0	245.0	563.0	115.0	57.1	172.1
	tibia	182.5	140.0	322.5	69.0	26.9	95.9
	fibula	—	—	57.0	—	—	13.2
	tarsals	—	—	160.6	—	—	39.2

TABLE III. A COMPARISON OF THE AMOUNT OF FAT CONTAINED IN THE BONES OF THE LOWER EXTREMITY

	Femur	
65-year-old woman (No. 13)		18-year-old man (No. 12)
51.9 Gm.	upper metaphysis	26.9 Gm.
57.1 Gm.	diaphysis	39.4
63.1 Gm.	lower metaphysis	55.3
172.1 Gm.	Total	121.6 Gm.
	Tibia	
69.0 Gm.	metaphyses	84.7 Gm.
26.9 Gm.	diaphysis	27.6
95.9 Gm.	Total	112.3 Gm.
	Fibula	
13.2 Gm.		12.0 Gm.
	Tarsals	
39.2 Gm.		46.8 Gm.
320.4 Gm.	Grand Total	292.7 Gm.

was surprisingly similar to that in the older patients, and well within the range of variation represented in the entire group. The chief discrepancy between the patients compared in Table III is in the fat content of the proximal metaphysis of the femur. Here, in the young man, the amount of fat is considerably less than that in the elderly woman. This can be explained by the observation that the proximal metaphysis of the woman contained only yellow marrow while in the man the marrow was grossly red and contained hematopoietic cells. All other portions of the bones contained only yellow marrow. Except for this one area, the comparison between these two extremities is remarkably close.

Of great interest is the distribution of fat within the long bone (Table II). The tubular diaphysis does not contain the major store of bone fat as assumed by Lehman and Moore. Instead, the spongy metaphysis with its greater volume contains the larger portion, for example, 60 per cent. If the figure of Lehman and Moore is considered to be accurate for the diaphyseal portion of the femur, the total fat content, with the addition of the metaphyseal fat, must be considerably greater. This variation between the fat content of the diaphysis and the metaphysis is due to the differences in the volume of the fatty marrow rather than in its concentration.

We have chosen to express our results by weight. The density of the extracted fat was determined in a pooled sample from the first 10 patients. At 37° C. the density was .901 Gm. per cubic centimeter. Using this density, and calculating the figures of Scriba, and Lehman and Moore in grams, their figures for the amount of fat contained in a human femur are 63 Gm. and 59 Gm., respectively. A glance at Table III clearly demonstrates how incompletely their figures represent the total amount of fat in the adult femur.

SUMMARY

The total amount of fat contained in human long bones was determined by extracting the entire bone with alcohol and ether. The major amount of bone fat was contained in the metaphyseal sponge rather than the diaphyseal tube. The quantities obtained were greatly in excess of those obtained by calculation, previously stated in the literature. From the data presented here it would appear that there is sufficient fat in the long bones to account for the phenomenon of fat embolism; the source of the emboli being the local site of injury.

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FAT EMBOLISM

II. The Chemical Composition of Fat Obtained From Human Long Bones and Subcutaneous Tissue

Leonard F. Peltier, M.D., Ph.D.,* Donald H. Wheeler, Ph.D.,**
Harold M. Boyd,*** and Joan Randolph Scott, Minneapolis, Minn.

(From the University of Minnesota and General Mills Research Department)

INFORMATION concerning the chemical composition of human bone fat is meager. During the process of determining the amount of fat in human long bones, large quantities of this material became available. The next step was to study its chemical composition.

PROCEDURE

Fat from human long bones was obtained by morcellating them and extracting the fat according to Bloor's method.[1] Details as to the source of this material are described elsewhere.[6]

Subcutaneous fat was obtained from the same specimens by a similar morcellation and extraction.

In order to characterize the fat, the following determinations were carried out:

1. Saponification Value: the number of milligrams of potassium hydroxide (KOH) required to saponify one gram of fat.[4a]
2. Iodine Value: the number of grams of I_2 absorbed by 100 Gm. of fat.[4b]
3. Acid Value: the number of milligrams of KOH required to neutralize the free fatty acids present in one gram of fat.[4c]
4. Unsaponifiable Matter: that portion of the fat which cannot be changed to water-soluble products by saponification (per cent by weight of original sample).[4d]
5. Unsaturated constituents were determined by ultraviolet spectrophotometry both before and after isomerization.[4e]
6. Oleic acid was determined by calculation from the Iodine Value and the determination of the per cent of other unsaturated constituents according to formula.[4f]
7. The per cent of saturated fatty acids was determined by a modification of Bertram's method.[5]

Fat analyses were carried out on samples from the metaphyses and diaphysis of the tibia in 5 patients and of the femur in 2. The remaining analyses were carried out on pooled samples of fat extracted from the whole bone.

RESULTS

The results of the analyses are presented in Tables I and II. The striking thing about the data is the similarity of the various values from sample to

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*Associate Professor and Acting Head, Division of Orthopedic Surgery, University of Minnesota.

**Principle Research Chemist, General Mills Research Department.

***Head, Analytical Section, General Mills Research Department.

TABLE I. CHARACTERIZATION OF FAT FROM HUMAN BONES AND SUBCUTANEOUS TISSUE OF PATIENTS OVER 60 YEARS OF AGE

PATIENT NUMBER	SOURCE OF FAT	SAPONIFICATION VALUE	IODINE VALUE	ACID VALUE	UNSATURATED FATTY ACIDS (PER CENT)				SATURATED FATTY ACIDS*	UNSAPONIFIABLE MATERIAL
					LINOLENIC	LINOLEIC	OLEIC	ARACHIDONIC		
1.	Tibia									
	Metaphyses	196	71.0	.34	.16	6.40	63.3	.61	26.5	.80
	Diaphysis	194	73.2	.34	.22	6.28	66.0	.56	26.9	.85
	Skin	198	79.1	.11	.36	7.03	63.0	.70	20.0	.59
2.	Tibia									
	Metaphyses	193	69.1	.49	.16	7.36	53.1	.66	38.7	1.81
	Diaphysis	195	69.8	.18	.11	7.14	60.5	.66	31.5	1.06
	Skin	196	72.5	.47	.33	7.18	57.2	.40	34.8	.82
3.	Tibia	197	74.2	.24	.24	8.28	63.0	.56	29.0	
	Skin	198	79.5	.78	.29	7.65	68.3	.51	23.2	
5.	Tibia	195	69.5	.20	.24	6.81	59.3	.66	33.0	
	Skin	196	78.0	.85	.26	7.51	62.0	.66	29.6	
6.	Tibia	196	70.5	.39	.10	8.20	59.4	.70	31.6	
	Skin	197	77.8	.71	.00	7.45	67.9	.98	23.7	
7.	Tibia	196	74.6	.48	.28	8.51	56.5	.56	34.2	
	Skin	198	79.0	1.70	.21	7.79	69.0	.70	22.0	
9.	Tibia	195	74.0	.35	.25	10.49	52.9	.52	35.8	
	Skin	197	80.7	.24	.30	10.39	58.8	.66	29.9	
10.	Tibia	194	76.0	.40	.00	7.55	65.2	1.10	22.0	
	Skin	197	73.7	11.41	.00	6.61	64.7	1.03	22.0	
13.	Femur									
	Metaphysis	197	71.8	.21	.26	8.73	59.8	.47	30.7	
	Diaphysis	194.1	68.2	.65	.11	9.00	55.8	.42	34.7	
	Tibia									
	Metaphysis	194.8	71.9	.13	.22	8.65	60.1	.47	30.6	
	Diaphysis	193.4	70.9	.17	.18	8.36	59.7	.47	31.3	
	Fibula	196.4	71.8	.24	.23	8.56	60.1	.42	30.7	
	Tarsals	195.0	72.9	.61	.30	8.49	61.4	.47	29.3	

*The underlined values for saturated fatty acids were obtained by a modification of Bertram's method; the others by calculation.

TABLE II. CHARACTERIZATION OF HUMAN FAT FROM LONG BONES AND SUBCUTANEOUS TISSUE IN YOUNG ADULTS (18 YEARS OLD)

PATIENT NUMBER	SOURCE OF FAT	SAPONIFICATION VALUE	IODINE VALUE	ACID VALUE	LINOLENIC	LINOLEIC	OLEIC	ARACHIDONIC	SATURATED FATTY ACIDS
11.	Tibia								
	Metaphyses	189.0	67.5	.22	.21	8.36	56.4	.33	34.7
	Diaphysis	186.7	65.6	.19	.26	7.95	55.2	.28	36.3
	Skin	192.3	71.8	.40	.26	8.12	61.6	.30	29.7
12.	Femur								
	Metaphyses	191.3	68.1	1.48	.25	9.46	54.9	.28	35.1
	Diaphysis	187.4	66.4	.78	.33	9.32	53.0	.28	37.1
	Tibia								
	Metaphyses	193.5	70.9	1.24	.45	9.52	57.4	.28	32.4
	Diaphysis	191.4	67.6	.91	.35	9.26	53.8	.42	36.2
	Fibula	195.2	72.2	2.16	.42	9.78	57.6	.47	31.7
	Tarsals	185.0	69.5	1.07	.46	9.21	56.3	.28	33.8
	Skin		74.4	1.73	.48	10.30	59.2	.38	29.6

sample. Only the Acid Values, the amount of free fatty acids in the untreated sample, show an appreciable variation. This is probably due to varying conditions of storage during the period from amputation to analysis and is a measure of the amount of hydrolysis of the neutral fat which has occurred.

There is no significant difference between the composition of the fat in the metaphyses and the diaphysis of the same bone, nor between the fat in different bones from the same individuals. The composition of bone fat in the distal portion of the limb, that is, the tarsals, is similar to that in the proximal portion, that is, the femur.

In comparing the composition of fat from individuals over 60 years of age and from individuals 18 years of age, no marked differences are seen. The Iodine Values in the 18-year-olds are consistently somewhat less. This is accounted for by a similar decline in the total amount of oleic acid and other unsaturated acids, and an increase in the amounts of saturated fatty acids. These differences are not great but are probably significant.

Fat extracted from the subcutaneous tissues of the leg closely resembles fat from the bone beneath. Here too, however, is a trend, this time toward a higher Iodine Value and a slightly greater amount of the unsaturated acids in the subcutaneous fat.

Fat obtained by the method of Bloor from human long bones and subcutaneous tissue consists almost entirely of neutral fat. Sixty-five to 80 per cent of the fatty acid constituents are unsaturated. The major portion of the unsaturated fatty acids consists of oleic acid.

DISCUSSION

In 1925, Eckstein[3] studied the composition of fat extracted from an 18-pound specimen of subcutaneous tissue obtained from a patient undergoing lipectomy. His data follows: nonsaponifiable matter, 0.37 per cent; unsaturated fatty acids, 63.6 per cent; saturated fatty acids, 26.6 per cent.

The unsaturated fatty acids consisted almost entirely of oleic acid with some other acids, especially linoleic, containing two, three, and four double bonds. His findings are very similar to ours.

In 1943, Cramer and Brown[2] studied the composition of fat extracted from tissue removed from the panniculus, the mesentery, and the perirenal areas of 5 patients, the youngest of whom was 53 years of age. The methods of analysis used were not the same as those used by us. The general agreement of their data with those reported here is surprisingly good. Cramer and Brown reported a slightly larger proportion of saturated fatty acids, and smaller amounts of unsaturated acids. This variation, however, is small.

It appears that fat, whether from the bone, subcutaneous tissue, or abdominal viscera, contains essentially the same proportions of constituents.

SUMMARY

It has been found that human fat obtained from the long bones and subcutaneous tissue does not differ markedly in composition. The fat from young adults is very similar to that from older individuals. This fat is almost entirely neutral fat. Unsaturated fatty acids comprise 65 to 80 per cent of the constituent acids, the remainder being fully saturated. Oleic acid is the most important constituent acid of human fat. Linoleic acid is present in small quantities; arachidonic and linolenic acids, in traces.

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FAT EMBOLISM

III. The Toxic Properties of Neutral Fat and Free Fatty Acids

Leonard F. Peltier, M.D., Ph.D., Minneapolis, Minn.

(From the Department of Surgery, Division of Orthopedic Surgery, The Medical School of the University of Minnesota)

IN OBSERVING patients exhibiting the classical form of fat embolism, that is, patients in whom symptoms appear after a latent period of twenty-four to forty-eight hours following injury, we have been impressed with two definite findings. Coincident with the appearance of the petechiae which help to establish the diagnosis, there is a sharp drop in the hemoglobin. This anemia is out of all proportion to the external blood loss or to the blood loss at the local site of injury. At the autopsy table, the lungs are heavy and filled, not with a transudate or simple pulmonary edema, but with whole blood, the result of intra-alveolar hemorrhage. These observations suggest that the mechanical obstruction of the lung capillaries by fat emboli may be only one phase of the disturbed physiology in this condition, while the chemical action of the fat or its constituents, producing disruption of the capillary bed, may represent another. Having determined that the bones contain large quantities of neutral fat, and that about 75 per cent of the constituent fatty acids is unsaturated, it was decided to investigate the toxic properties of neutral fat and free fatty acids.

MATERIALS

Chemically pure triolein, and oleic, linoleic, and linolenic acids were obtained in ampules containing nitrogen.*

Human fat was obtained from a pooled sample of fat from ten human tibiae.[13] The chemical composition of the individual samples had been determined previously.[14] A portion of this fat was saponified. The fat was boiled in a solution of 50 per cent potassium hydroxide (KOH) in 70 per cent alcohol for one hour using a reflux condenser. The unsaponifiable matter was removed by extracting the alkaline solution with petroleum ether. The solution was then adjusted to pH 3.0 by the addition of hydrochloric acid. The fatty acids were obtained by extracting this solution with petroleum ether and then evaporating the ether.

PROCEDURE

Adult rabbits weighing 2 to 4 Kg. were used in all experiments. No anesthesia was required. All materials were administered, without additives or diluents, intravenously via the ear veins, the time of injection being no greater than 15 seconds. Dosage was calculated in milligrams per kilogram of weight. All surviving animals were sacri-

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ficed with intravenous injections of sodium pentobarbital. The animals were autopsied; the lungs, brain, and kidney preserved in formalin. Frozen sections of these organs were stained with Sudan III, phosphin 3R,[12] and hematoxylin and eosin.

The LD_{50} was determined for the intravenous injection of human fat, triolein, mineral oil, oleic, linoleic and linolenic acids, and saponified human fat. The end point used in calculating the LD_{50} was death of the animal occurring within three hours following the injection. One hundred twenty rabbits were used in these experiments.

TABLE I. THE LD_{50} OF NEUTRAL FAT AND FATTY ACIDS FOR RABBITS (SINGLE INJECTION, 15 SECONDS' DURATION)

MATERIAL	LD_{50} (MG. PER KG.)
Human fat	900
Triolein	900
Mineral oil	500
Saponified human fat	225
Oleic acid	250
Linoleic acid	225
Linolenic acid	200

RESULTS

The LD_{50} determinations are shown in Table I.

There was a very distinct difference between the behavior of those animals injected with neutral fat, and those injected with free fatty acids. After the injection of mineral oil, human fat, or triolein, the rabbits became dyspneic, the ear veins became engorged with blood and occasionally some white foam appeared at the nose and mouth. Sudden death, less than one minute after injection, could not be produced by using larger doses than the LD_{50}. At autopsy the striking findings were (1) the tremendous dilation of the right heart, and (2) the anemia of the lungs (Fig. 1). The right ventricular wall was thin and flabby. The tracheobronchial tree was filled with white froth. The lungs did not collapse upon removal, but appeared to be slightly distended. The weight of the lungs was slightly increased above normal.

Fig. 1.—Rabbit lungs. The specimen on the left is from a rabbit dying after the injection of triolein (900 mg. per Kg.). Note the anemia. The specimen on the right is from a rabbit dying after the injection of oleic acid (250 mg. per Kg.). Note the hemorrhagic appearance.

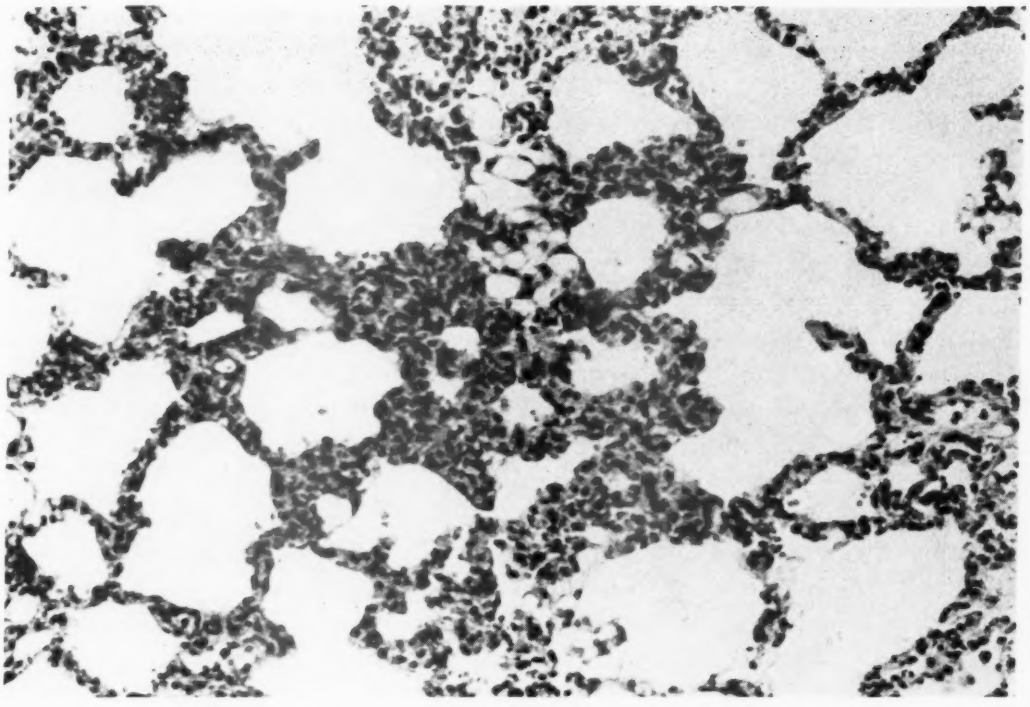

Fig. 2—Section of lung from rabbit dying after the injection of triolein (900 mg. per Kg.). There is some congestion, but the alveolar pattern remains intact.

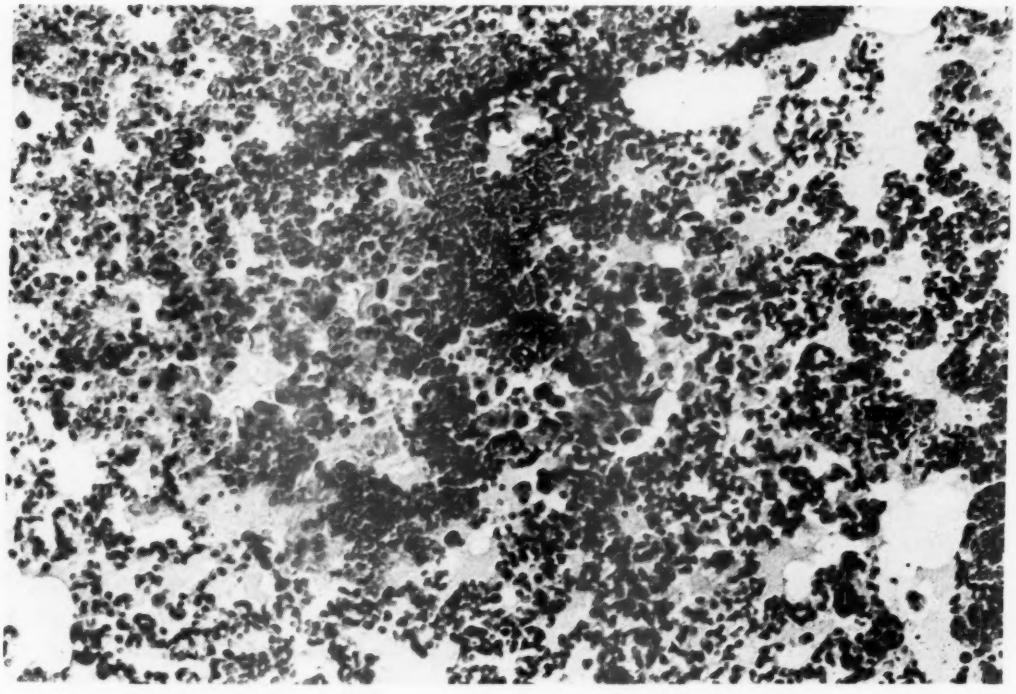

Fig. 3.—Section of lung from rabbit dying after the injection of oleic acid (250 mg. per Kg.). Note the congestion, hemorrhagic exudate, and disorganization of the alveolar pattern.

There was very little blood in them. They appeared dead white with rare small hemorrhagic areas immediately under the pleural surfaces. Sections of these lungs stained with hematoxylin and eosin confirmed these observations (Fig. 2). There was little blood in the lungs and none in the alveoli. Occasionally some alveoli were noted to be filled with a clear transudate or edema fluid. These findings indicate that these animals died of acute right heart failure as a result of the *mechanical obstruction* of the arterioles of the pulmonary vascular bed.

Following the injection of saponified human fat or oleic, linoleic, and linolenic acids, dyspnea appeared more slowly and was accompanied by a profuse drainage from the nose and mouth of red, bloody froth. In about 10 per cent of the animals, death was immediately preceded by a convulsion and marked opisthotonos. By increasing the dosage above the LD_{50}, sudden death, in less than one minute after injection, could be produced. At autopsy the heart was not markedly dilated. The lungs were engorged with blood, weighing 2 to 3 times their normal weight. The tracheobronchial tree was filled with bloody foam. Gross blood dripped from the pleural surfaces. Histologic examination showed alveoli filled with bloodstained exudate and whole blood. The alveolar structure in many areas had completely disintegrated (Fig. 3). These findings indicate that these animals died as a result of hemorrhage into the lung due to the *chemical action* of the fatty acids upon the capillary endothelium with resulting exudate and hemorrhage.

DISCUSSION

The difference between the LD_{50} for human fat and triolein, and mineral oil cannot be explained on their chemical properties since they are all chemically inactive. The difference is due to a difference in mechanical properties, that is, their viscosity. The viscosity of human fat at 37° C., as determined with an Ostwald viscosimeter, was 29.8 c.p.; of mineral oil, 47.2 c.p. The viscosity of water under similar conditions was 0.68 c.p. The greater viscosity of the mineral oil enhances its ability to produce mechanical obstruction in the vascular bed and satisfactorily explains its greater toxicity as compared to human fat and triolein.

The anemia associated with fat embolism has been noted by several authors,[4, 7, 10, 18] as well as by ourselves. It does not appear immediately but rather after the first twenty-four to forty-eight hours; in other words, after the so-called latent period. The location of this intracorporeal hemorrhage is not the local site of injury but the lungs. This can be confirmed at autopsy. The cause of the hemorrhage is not the mechanical obstruction of the vascular bed. It is due to the action on the capillary endothelium of the fatty acids freed by hydrolysis from the emboli of neutral fat. This view is in accord with Newman,[11] who felt that the pathologic findings in fat embolism could not be explained on the basis of simple obstructive embolism alone.

TABLE II. RESULTS OF PREVIOUS INVESTIGATIONS OF THE TOXIC PROPERTIES OF NEUTRAL FAT AND FATTY ACIDS

AUTHOR	MATERIAL	ANIMAL	RESULT (C.C. PER KG.)
Scuderi[17]	Olive oil	Dog	†MLD 2.20
	Oleic acid	Dog	MLD 0.33
Harris and associates[7]	Human fat	Rabbit	MLD 0.9
	Hydrolyzed human fat	Rabbit*	MLD 0.07
Elkes[5]	Oil	Rabbit	MLD 1.02
	Fat from adipose tissue	Rabbit	MLD 0.93
	Fat from bone marrow	Rabbit	MLD 0.9
	Oleic acid	Rabbit	MLD .13

*Noted severe pulmonary hemorrhagic exudate.
†MLD—minimum lethal dose.

Others have investigated the relative toxicity of neutral fats and fatty acids. A summary of their work is shown in Table II. Their results are in general agreement with those reported here.

The toxicity of neutral fats is a function of their viscosity. The toxicity of the various fatty acids is a function of the degree of unsaturation; that is, their chemical activity. Stearic acid was not investigated because it is not liquid at body temperature. However, it would appear that it would be less toxic under the conditions of this experiment than is oleic acid.

Hirsch[9] studied the reaction of tissues to lipids introduced into them. The presence of unhydrolyzed fat provoked a reaction comparable to that of an inert oil. Hydrolysis introduced a chemical factor. The glycerol, being water soluble, rapidly dffuses away without effect. The free fatty acids remaining behind produce a severe inflammation. Hagerty[6] used human fat, mineral oil, and oleic acid to produce experimental glomerulonephritis in animals. These substances were injected directly into the renal arteries. Oleic acid produced small cortical hemorrhages; human fat, moderate glomerular changes over a long period of time; mineral oil, very little change. Pinkerton[15] found that the reaction of the lung to intratracheally administered oil was directly related to the amounts of free fatty acid present in the oil.

This toxic action of the free fatty acid in the alkaline aqueous medium of the body tissues or blood may be due to the fact that basic ions are removed and H^+ is released; the tissue necrosis resulting from the local acidity.[9] The tremendous buffering properties of the body fluids make this mechanism seem unlikely.

It is more probable that the site of action is at the intercellular junction. Butcher[1-3] has shown that the application of free fatty acids to the skin increases the permeability of the epithelium tremendously. The more unsaturated the acid, the greater the effect. Robertson[16] has shown that intercellular cohesion is related to the action of calcium ions. Free fatty acids have an affinity for calcium ions and form calcium soaps. This affinity is great enough to produce tetany in patients with acute pancreatitis with massive fat necrosis.[8] It may be that the immobilization of the calcium ions

results in a loss of intercellular cohesion with a consequent disruption of the epithelial, or in the case of fat embolism, in the endothelial surface of the capillaries. Hemorrhage into the alveoli or other pericapillary tissues results.

The relationship between these studies and the problem of fat embolism lies in the fact that the long bones contain large quantities of neutral fat. The fatty acids which are the major constituents of this fat are those investigated here. The appearance of the lungs of patients with the classical findings of fat embolism closely resemble the lungs of animals damaged by the injection of these fatty acids.

SUMMARY

The toxicity of neutral fats and mineral oil is a function of their viscosity. Death following the intravenous injection of these substances is due to the mechanical obstruction of the pulmonary vascular bed. The toxicity of free fatty acids is a function of the degree of unsaturation, that is, their chemical activity. Death following the intravenous injection of these substances is caused by a disruption of the capillary endothelium caused by their chemical action. This action may be the result of the affinity of the fatty acids for calcium ions.

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METABOLISM IN SURGICAL PATIENTS

III. Effect of Drugs and Dietary Procedures on Fat and Nitrogen Metabolism in Totally Gastrectomized Patients

Morton K. Schwartz, Ph.D., Oscar Bodansky, M.D., and Henry T. Randall, M.D., New York, N. Y.

(From the Surgical Metabolism Section, Division of Experimental Surgery, Sloan-Kettering Institute; the Department of Surgery, Memorial Center; and the Sloan-Kettering Division, Cornell University Medical College)

PERSONS who have undergone total gastrectomy usually present a picture of gross undernutrition. They are unable to regain their preoperative weight, experience distress after eating, and lose a considerable amount of ingested fat and nitrogen in their stool. The present study is concerned with the extent to which various substances or various procedures that effect gastrointestinal function alter the absorption of fat and nitrogen.

METHODS AND MATERIAL

The metabolic and chemical methods used in this study have been described elsewhere.[14, 15] When a dietary adjuvant was used, it was analyzed in the laboratory for fat and nitrogen and the values were added to the regular dietary intake. The U.S.P. pancreatin powder used in these studies will convert not less than 25 times its weight of casein to proteoses and not less than 25 times its weight of potato starch to soluble carbohydrate.[13] Pulverized "triple strength" pancreatin tablets and the VioBin pancreas used in the study were analyzed for proteolytic activity by the method of Anderson[1] and for lipolytic activity by the method of Goldstein.[6] One gram of VioBin pancreas contained proteolytic activity equivalent to 50 mg. of crystalline trypsin* and 934 tributyrinase units of lipolytic activity. One gram of the pulverized "triple strength" pancreatin contained the equivalent of 5.2 mg. of trypsin per gram of powder and 273 tributyrinase units. The purified lipase† used in the study was analyzed for lipolytic activity and found to have 719 tributyrinase units per gram of powder. According to the method used here, a tributyrinase unit is the amount of enzyme that will lead to the release of 1 ml. of 0.1N fatty acid in one hour at 37° C. from an aqueous emulsion of 0.25 c.c. of tributyrin in 0.25 per cent diethylbarbiturate buffer containing 1 per cent calcium acetate as an activator.

Of the 9 patients included in this study, 2, J. B. and B. B., had an esophageal reconstruction for carcinoma of the esophagus and 2, B. M. and J. K., had total gastrectomies for large benign gastric ulcers. Of the remaining 5, N. F. had a lymphosarcoma and B. S., a leiomyosarcoma; the other 3, ordinary mucosal carcinomas of the stomach. All were free of recurrent disease as far as could be determined. One patient, B. S., developed symptoms at six months and died one year following the study with metastases to the liver. All the

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*Mann Chemicals.

†Fisher Scientific Company.

others are apparently free of recurrences up to two years after study. The patients described had undergone operation from seventy-five days to four years before study and had recovered from their operative trauma.

Although an attempt was made to determine the effects of the various dietary adjuvants in as many cases as possible, the individual patient was very often a limiting factor in these studies.

RESULTS

Pancreatin.—In Table I the effect of pancreatin on the fat and nitrogen metabolism of 6 gastrectomy patients with steatorrhea is shown. U.S.P. pancreatin powder was administered to 2 of the patients, J. R. and J. K., in daily doses of 18 and 9 Gm., respectively. Pulverized "triple strength" enteric coated tablets were taken in a daily dose of 18 Gm. by 3 patients, B. M., A. S., and J. M. One patient, N. F., received 18 Gm. per day of a four times U.S.P. strength pancreas preparation made by the VioBin Corporation. The preparation used was given in equally divided amounts with the morning, noon, and evening meals. The fecal nitrogen excretion was not affected by pancreatin in any of the forms tried. In all cases there was a moderately severe steatorrhea, and the added pancreatic enzymes did not improve fat absorption. In fact, in most of the cases (B. M., B. S., J. K., G. M.), there seemed to be a slight increase in fecal fat when the pancreatin was taken.

TABLE I. EFFECT OF PANCREATIN ON FAT AND NITROGEN EXCRETION BY TOTALLY GASTRECTOMIZED PATIENTS

		NITROGEN				FAT		
PATIENT	DOSE AND TYPE OF PANCREATIN (GM./DAY)	INTAKE (GM.)	URINE (GM.)	STOOL (GM.)	BALANCE (GM.)	INTAKE (GM.)	STOOL (GM.)	PER CENT OF INTAKE EXCRETED
B. M.	0	10.2	6.5	2.0	+1.7	72.3	10.0	13.8
	18 (3 × U.S.P.)	10.8	7.3	2.1	+1.4	72.3	12.4	17.2
A. S.	0	8.0	7.4	1.8	-2.1	62.9	18.2	29.0
	18 (3 × U.S.P.)	8.4	8.4	2.1	-2.1	62.9	21.3	33.9
J. R.	0	11.2	12.1	1.8	-2.7	172.9	33.2	19.2
	15 (1 × U.S.P.)	12.1	11.4	1.8	-1.1	172.9	32.1	18.6
J. K.	0	12.5	12.0	3.2	-2.7	143.1	31.1	21.7
	9 (1 × U.S.P.)	12.8	12.8	3.6	-3.6	143.1	39.3	27.5
G. M.	0	12.6	10.9	2.9	-1.2	90.8	19.6	21.6
	18 (3 × U.S.P.)	13.2	11.7	2.8	-0.5	90.8	26.3	29.0
N. F.	0	15.5	12.9	2.3	+0.3	84.8	28.6	33.8
	18 (4 × U.S.P.)	17.5	13.2	2.6	+1.7	84.8	29.3	33.6

Lipase.—In an attempt to increase fat absorption, the most important nutritional defect following total gastrectomy, purified lipase was given to 3 of the patients with steatorrhea. The dose was 6 Gm. at each meal. Table

II shows the effects of lipase on fat and nitrogen absorption. In one patient (A. S.) there appeared to be a beneficial effect on fat absorption and the fecal fat was reduced from 18 Gm. to 11 Gm. per day. However, in the 2 other patients to whom lipase was given (G. M. and N. F.) the lipase caused a severe diarrhea with increases in both fecal nitrogen and fecal fat.

TABLE II. EFFECT OF LIPASE ON FAT AND NITROGEN EXCRETION BY TOTALLY GASTRECTOMIZED PATIENTS

		NITROGEN				FAT		
PATIENT	DAILY DOSE (GM.)	INTAKE (GM.)	URINE (GM.)	STOOL (GM.)	BALANCE (GM.)	INTAKE (GM.)	STOOL (GM.)	PER CENT OF INTAKE EXCRETED
A. S.	0	8.0	7.4	1.8	-1.2	62.9	18.2	29.0
	18	10.1	9.2	1.2	-0.3	62.9	11.1	17.8
G. M.	0	12.6	10.9	2.9	-1.2	90.8	19.6	21.6
	18	14.7	12.6	2.9	-0.8	90.8	27.8	30.6
N. F.	0	15.5	12.9	2.3	+0.3	84.8	28.6	33.8
	18	17.6	12.1	4.7	+0.8	84.8	52.8	62.4

Tweens.—According to Frazer[4] absorption of fat depends chiefly on particle size. Unhydrolyzed fat may be absorbed from the intestine when it is present in a finely emulsified state. A system in which the fat particles are dispersed to 0.5 μ or less is necessary for this type of fat absorption. The emulsifier, polyoxyethylene sorbitan monooleate (Tween 80) has been reported by Jones and his associates[7] to facilitate fat absorption in patients who had fat absorption defects due to subtotal gastrectomy or sprue. Therefore, Sorlate* was given to 2 patients who had a steatorrhea in an effort to increase fat absorption by increasing fat emulsification. The dose was 6 Gm. per day given in three equal doses before meals. As can be seen in Table III there was no decrease in fecal fat or nitrogen on this regimen.

TABLE III. EFFECT OF TWEEN 80 ON FAT AND NITROGEN EXCRETION BY TOTALLY GASTRECTOMIZED PATIENTS

		NITROGEN				FAT		
PATIENT	DAILY DOSE (GM.)	INTAKE (GM.)	URINE (GM.)	STOOL (GM.)	BALANCE (GM.)	INTAKE (GM.)	STOOL (GM.)	PER CENT OF INTAKE EXCRETED
B. M.	0	10.2	6.5	2.0	+1.7	72.3	10.0	13.8
	6	10.1	7.6	1.5	+1.0	72.2	10.5	14.5
J. K.	0	12.5	12.0	3.2	-2.7	143.1	31.1	21.7
	6	12.5	12.3	4.4	-4.2	143.1	34.7	24.3

Intestinal Motility.—It has been stated that increased intestinal motility after gastrectomy is one of the main causes of the defect in absorption.[3, 5, 16] In one patient, J. K., a daily dose of 750 mg. of C-6 (hexamethonium bromide), an anticholinergic drug, was given in an effort to increase absorption by decreasing intestinal motility. There was no improvement in fat or nitrogen absorption. On a daily fat intake of 98.9 Gm., the fecal fat was 23.3 Gm.

*Abbott Laboratories' Sorbitan monooleate polyoxyethylene derivative.

without C-6 and 25.3 Gm. per day when the drug was taken. The fecal nitrogen on an intake of 21.6 Gm. per day was 2.5 Gm. during the control period and 3.5 Gm. per day during the period when hexamethonium bromide was taken. In this same patient, a left splanchnicectomy and resection of T-11 and T-12 of the sympathetic chain was performed. A metabolic study before and eleven days after surgery indicated that this procedure had not facilitated fat or nitrogen absorption. The fat intake was 64.5 Gm. per day; the stool fat 12.3 Gm. per day before operation and 12.2 Gm. per day after surgery. The nitrogen intake in both periods was 24.6 Gm. per day; the fecal nitrogen was 3.2 Gm. before surgery and 3.4 Gm. per day after the operation.

Role of the Stomach.—The importance of the intact stomach in nitrogen and fat absorption was studied in 2 patients who had undergone a Robertson-Sarjeant procedure for reconstruction of the esophagus.[12] Most of the esophagus had been removed, and the cephalad portion of the esophagus was connected to the jejunum by means of a jejunal inverted Y segment. When food is taken by mouth the stomach and duodenum are by-passed. Food may also be taken through a gastrostomy opening. Table IV shows that the fecal excretion of fat was increased when food was taken orally and thus by-passed the stomach. In Patient J. B., the fecal nitrogen excretion was within normal limits through either pathway. In B. B., the fecal nitrogen excretion was elevated moderately above the normal range when food was taken orally and was not significantly decreased in the following period when the food was introduced directly into the stomach.

TABLE IV. FAT AND NITROGEN EXCRETION IN PATIENTS WITH ROBERTSON-SARJEANT OPERATION

		NITROGEN				FAT		
PATIENT	TYPE OF FEEDING	INTAKE (GM.)	URINE (GM.)	STOOL (GM.)	BALANCE (GM.)	INTAKE (GM.)	STOOL (GM.)	PER CENT OF INTAKE EXCRETED
J. B.	Oral	10.6	8.2	2.3	+0.1	90.2	20.3	22.5
	Gastrostomy	10.6	7.2	1.1	+2.3	90.2	2.1	2.3
B. B.	Oral	16.1	7.3	4.2	+4.6	103.0	26.4	26.4
	Gastrostomy	16.1	8.4	3.5	+4.2	103.0	16.1	16.1

The above experiments raise the question whether the gastric mucosa or muscle contains any substances which affect fat absorption. In this connection it was of interest to determine the effect of a defatted, dessicated hog stomach preparation* which is stated to contain in a stable form the enzymes and other biologic substances in gastric mucosa and muscle. In Patient N. F., on a control period on a dietary intake of 84.8 Gm. of fat, the fecal fat excretion was 28.6 Gm. per day. The addition of 18 Gm. per day of the hog stomach powder gave a fecal fat excretion of 30.7 Gm., not significantly different from that of the control period.

Frequent Feeding.—In an attempt to simulate the gastric function of introducing small amounts of food into the intestine over a period of time a

*VioBin Corporation.

schedule of 8 instead of 3 feedings per day was used in metabolic studies in two patients. In one patient, this regimen led to a moderate decrease in fecal fat, from 28.6 Gm. per day to 20.5 Gm. per day; the absorption was thus increased from 66 per cent to 76 per cent of the dietary intake. When the patient was returned to 3 feedings per day, his fecal fat increased to 27.8 Gm. per day. In the second patient, on a fat intake of 89.6 Gm. during the 3 feeding period, the fecal fat was 12.7 Gm. per day, an absorption of 86 per cent. During the 8 feeding schedule, the fat intake was 114.0 Gm. per day and the fecal fat 14.2 Gm. per day, yielding an absorption of 88 per cent, not significantly different from that of the control period.

DISCUSSION

The results that have been presented in this study are of interest with respect to the genesis of steatorrhea following gastrectomy, a problem which has been considered by many earlier investigators.[2, 3, 8-11] Steatorrhea is conceivably due to one or more of the following factors: (a) Decreased stimulation of pancreatic secretion, (b) inadequate mixing of food with these secretions, since, as a result of the operation, the pancreatic secretions empty into the "dead-end" duodenum, whereas the food passes directly from the esophagus into the jejunum, (c) a deficiency of pancreatic enzymes, particularly lipase, since the operative procedure for gastrectomy frequently involves removal of part of the pancreas, (d) decreased emulsification, (e) increased intestinal motility, and (f) loss of stomach functions, such as triturating action and control of the flow of small amounts of chyme into the intestine. We may examine the extent to which earlier evidence and that presented here support these various hypotheses.

If one or more of the first three factors causes the steatorrhea, then the administration of pancreatin should tend to decrease the fat losses. Indeed, Rekers and his associates[11] have reported one patient, and Everson[3] has reported a second patient, with a total gastrectomy in which the daily administration of about 25 Gm. of pancreatin caused a substantial decrease in the excretion of fat. Everson[3] was unable to obtain any reduction in the excretion of fat in 12 totally gastrectomized dogs on a daily dose of 10 Gm. of pancreatin.

In our study, the administration of pancreatin preparations in dosages ranging from the equivalent of 9 Gm. to 72 Gm. of U.S.P. pancreatin did not alter the fat or nitrogen excretion significantly in any of 6 patients. These results therefore are not consistent with those obtained in the 2 patients reported in the literature. It is difficult to explain this discrepancy. Of the 6 patients in the present study who were given pancreatin, 5 had varying portions of the tail and body of the pancreas removed in the operative procedure and therefore did not differ in this respect from the patient of Everson.[3] Since the action of pancreatin on fat absorption is mediated through its content of lipase, the effects of this enzyme were studied and, as we have seen, decreased the steatorrhea in only one of 3 patients.

Emulsification has been held to play an essential role in the absorption of fat either according to the lipolytic theory or the partition theory. Jones[7] reported that Tween 80 caused decreases of varying magnitudes in the fat excretion in each of 5 patients with subtotal gastrectomy. As we have shown, we were unable to find such a decrease in either of 2 totally gastrectomized patients.

Although it has been stated that increased intestinal motility is one of the main causes of the defect in absorption of fat,[3, 5, 16] few data concerning this factor are available in the literature. Wollaeger[16] reported one partially gastrectomized patient in whom the administration of 0.65 mg. of atropine 4 times a day by mouth caused a definite decrease in fat excretion. Glazebrook and Welbourn[5] have reported one totally gastrectomized patient and one partially gastrectomized patient in whom the administration of 250 mg. of hexamethonium bromide before meals similarly caused a definite decrease in the excretion of fat. Our results with hexamethonium bromide and left splanchniectomy in a single patient are not in agreement with these previous reports, but it is possible that the intestinal motility was not affected in our patient.

The results presented in this report indicate that the stomach as such plays some role in fat absorption. Each of the 2 patients who had had a Robertson-Sarjeant[12] procedure for reconstruction of the esophagus showed less fat excretion when food was passed through the stomach than when it went from the esophagus to the jejunum. The increased fat excretion when the stomach was by-passed could be ascribed either to the absence of the stomach or the by-passing of the duodenum with its pancreatic secretions. We, however, have seen that the excessive fat excretion in our totally gastrectomized patients was not readily attributable to a pancreatic deficiency or a failure of the pancreatic secretions to mix with the food contents. Hence, it would appear that the improved fat absorption resulting from the introduction of food into the stomach in patients with the Robertson-Sarjeant procedure is due to the stomach itself.

The exact manner in which the stomach plays a beneficial role remains obscure. Our experiments with frequent feeding or the effect of dessicated hog stomach or other stomach preparations are not extensive enough to furnish information on this point.

SUMMARY

1. Pancreatin, lipase, Tween 80, hexamethonium bromide, splanchniectomy, and dessicated hog stomach were not effective in reducing the fecal fat or nitrogen excretion in totally gastrectomized patients.

2. The importance of the intact stomach was demonstrated in 2 patients who had undergone the Robertson-Sarjeant[12] procedure for reconstruction of the esophagus. In these patients the excretion of fat and nitrogen was less when the food was passed through the stomach than when it went directly from the esophagus to the jejunum.

3. A frequent feeding regimen decreased the fat excretion in one of the 2 totally gastrectomized patients in whom this procedure was tried.

The work was done in active cooperation with the Gastric Service of the Department of Surgery of Memorial Center, and in particular with Drs. Gordon McNeer and George Pack, many of whose private patients are included in this study and without whose help this work could not have been done. We are also indebted to Dr. John Madden for referring Patient N. F. to us.

Patients on whom these metabolic studies were conducted were a part of a group of patients being studied clinically by the Surgical Physiology Group under the supervision of Dr. Kathleen Roberts. Other aspects of the problem of total gastrectomy are being presented by other members of this team in papers in press at this time.

As is the case in all metabolic studies, this work would not have been possible without the devoted aid and assistance of our technical, dietary, and nursing staff, including Mrs. G. Gray, and Miss Pat Timbol (technicians); Mrs. M. Turi, Miss M. O'Connor, and Miss C. Coti (nursing staff); and Mrs. L. Stroub, Mrs. R. DeSimone, Mrs. J. Schwartz, and Miss B. Scaglione (dietitians).

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THE PREVENTION OF ILEOSTOMY DYSFUNCTION

JOHN H. GARLOCK, M.D., AND PAUL A. KIRSCHNER, M.D., NEW YORK, N. Y.

(From the Surgical Service of The Mount Sinai Hospital)

DURING the past twenty years, there has taken place an increasing interest in the surgical treatment of idiopathic ulcerative colitis. Not only have the indications for surgical intervention been more clearly defined, but also there has occurred a diminishing antagonism on the part of the medical profession as well as the lay public to the idea of a permanent ileostomy. The phenomenal physical and psychological rehabilitation that follows ileostomy and colectomy in the vast majority of patients has influenced the judgment of some surgeons to the extreme of advising surgical therapy for most, if not all, patients with ulcerative colitis. On the other hand, there still remains a large segment of the medical profession which maintains that ileostomy should be carried out only as a last resort. That the intelligent approach lies somewhere between these two extremes seems obvious and hardly needs further comment.

In the wake of increasing experience with the surgical treatment of ulcerative colitis has come a group of complicating factors inherent in the surgical maneuvers themselves which have forced the surgeons to pause and attempt to clarify the reasons and institute corrective therapy. By far the most important among these is dysfunction of the ileostomy, a term introduced by Warren and McKittrick in 1951.[26] In fact, it is possible that the high incidence of ileostomy difficulties may be a large factor in the antagonism of many members of the medical profession to the surgical treatment of colitis. We would like to relate our experiences with this complication in a large group of patients and to suggest an operative regimen in the fashioning of an ileostomy which has all but eliminated the difficulties so commonly encountered heretofore.

The symptom complex of ileostomy dysfunction is rather clearly defined and should be recognized with ease. Within a few days after operation, there will be noted the onset of cramplike abdominal pain accompanied by an increase in the volume of ileostomy discharge which then assumes a watery consistency. There may be vomiting, increased abdominal distention, and the rapid appearance of a shocklike state which has been proved to be due to a sudden severe water and electrolyte depletion. Although this clinical picture may appear at varying times after operation, it is most often encountered between five and twelve days postoperative. The patient becomes listless, cries out with each bout of cramps, and may rapidly reach a state of irreversible shock. We recall in the early days of our experience a young man who developed one of these episodes on the fifth day and who died within six hours of its onset. The need for urgent fluid and electrolyte replacement was not appreciated at the time, and it is

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probable that quick action would have been lifesaving. It must be emphasized that nowadays, because of our better understanding of water and electrolyte metabolism in the postoperative care of patients, it is rare to encounter this extreme phase of ileostomy dysfunction. But it cannot be denied that lesser degrees of this disturbance are all too frequent and make for a complicated and prolonged convalescence. Warren and McKittrick[26] reported in 1951 an incidence of 61.9 per cent. In our own series of cases, the incidence of ileostomy dysfunction was close to 40 per cent.

There seems little doubt that the basic cause of this disturbance of ileostomy function is a partial obstruction of the ileostomy itself, either at the exteriorized site or in the terminal one or two feet within the abdomen. This has given rise to the practice of intubating the ileostomy for varying periods of time until the obstruction is corrected and the ileal flow becomes greenish-yellow in color and thicker in consistency. However, there is no unanimity of opinion as to the exact cause of the obstruction. We believe that the theory proposed by Crile and Turnbull[9] is the most logical one advanced so far and corroborates many clinical observations that we have made over the past decade. Their explanation emphasizes the fact that an unprotected segment of ileum is brought out of the abdomen and is immediately exposed to the septic contents of its own discharges. There is initiated an infection of the peritoneal covering of the ileum, with exudate, edema, rigidity, and loss of peristalsis. It is stated that an end ileostomy must progress through certain phases before it begins to function normally and to this sequence of events they apply the phrase "maturation of the ileostomy." During this period, the infected serosal surface slowly contracts until the mucosal edge is pulled backwards to the abdominal skin. It may be four to eight weeks before this process is completed.

While we agree thoroughly with the essence of this theory, we believe Crile and Turnbull have not gone far enough. From our observations at the bedside and at secondary operations for the correction of ileostomy dysfunction, we are of the opinion that the serositis or low grade peritonitis which begins at the exteriorized segment may extend *within the abdomen* and involve segments of terminal ileum of varying lengths producing fibrinous adhesions and partial obstruction to the normal flow of ileal contents. Even in the absence of the serositis described by Crile and Turnbull, there will not infrequently be found instances of kinking of the terminal twelve to twenty-four inches of ileum requiring intubation either through the stoma or from above by a Cantor or similar tube. We are of the opinion that any operation devised to prevent all the varieties of ileostomy dysfunction must include a maneuver which will obviate this intra-abdominal complication.

In order to eliminate all possibility of the serositis which so frequently follows the classical end-ileostomy operation, Turnbull[25] devised a complicated procedure which, in essence, consists of excision of the seromuscular layer of the terminal inch of ileum and eversion of the remaining mucosal-submucosal remnant with suture of its edge to the skin margin. While we agree with the original premise which produced the idea of this operation, we believe it to be unnecessarily complicated, prone to technical accidents, and subject to inherent

complications. The same result can be accomplished by the much simpler eversion maneuver of the whole thickness of the ileal wall described by Brooke[3] of England in 1952.

The statement has been made that since the advent of the operation of ileostomy and colectomy in one stage, as advocated by Gavin Miller,[22] the incidence of ileostomy dysfunction has been greatly diminished. Nothing could be further from the truth. On the contrary, there is evidence to indicate that the reverse is true. It is not our intention to embark upon a discussion of the relative merits of the single stage or multiple stage operations for ulcerative colitis, but the evidence is clear that in recent years more patients have been better prepared for a single stage operation than was possible in the past. We believe also that there are definite indications for ileostomy alone. Ulcerative colitis is one disease, par excellence, where the old adage "make the operation fit the patient" is particularly applicable. It is disturbing to see how often "the patient is being made to fit the operation."

TECHNIQUE OF OPERATION

Before operation, the site of the permanent ileostomy must be carefully chosen and indicated on the abdominal wall with indelible dye. In so doing, the surgeon must take into account a number of important factors: (1) The ileostomy must be located on a smooth surface of the abdominal wall in order to have a firm application of the flange of the ileostomy bag, taking into account the eventual considerable weight gain. (2) The ileostomy should not be near any bony prominences or the umbilicus. (3) The ileostomy should not be placed in an operative incision, because the possibility of wound infection is greatly augmented and because the bag flange will not fit snugly on a scarred incision. (4) The ileostomy should be placed in such a way as to offer some degree of symmetry for the fully-clothed patient after application of the bag. Experience has taught us that all these criteria can be met if the ileostomy site is located on the right side of the abdomen about midway between the anterior spine of the ilium and the umbilicus, near the outer third of the rectus muscle. We believe this to be the most desirable location. Of course, complicating factors such as abdominal wall fistulas may force the surgeon to place the ileostomy elsewhere, but this does not happen too often.

If the decision has been made to do an ileostomy only, the major approach is through a vertical left rectus incision opposite the umbilicus. Should the surgeon change his mind and wish to proceed with colectomy also, then this primary incision can be enlarged to the necessary length. With appropriate lateral and forward retraction of the right part of the incision, the terminal ileum is isolated and carefully inspected for intrinsic disease. It is best to transect the ileum at least 12 inches proximal to the ileocecal valve in order to exclude any possibility of so-called "back wash" ileitis. We have on occasion excluded at least 3 feet of terminal ileum in order to insure normal bowel for the ileostomy site. By holding the mesentery up to the light, the vascular arcades can be clearly delineated and ligated individually so as to avoid bunching of the cut mesenteric edge and to insure an adequate blood supply for the

ileostomy limb. The incision in the mesentery should be quite deep in order to assure sufficient length for exteriorization of at least 2½ to 3 inches beyond the skin surface without tension. If no colectomy is to be done at this stage, a DeMartel-Cope clamp is placed on the distal segment, a small Payr clamp on the proximal end and the bowel is divided between the two with a carbolic knife. The distal limb is then brought out through a small right McBurney incision to act as a vent for accumulated secretions. A button of skin about one inch in diameter is now excised at the site selected for the permanent ileostomy. The incision in the fascia is crisscrossed and the fibers of the rectus muscle are separated in a vertical direction. At times it may be necessary to ligate the epigastric vessels. The peritoneum at this site is incised vertically.

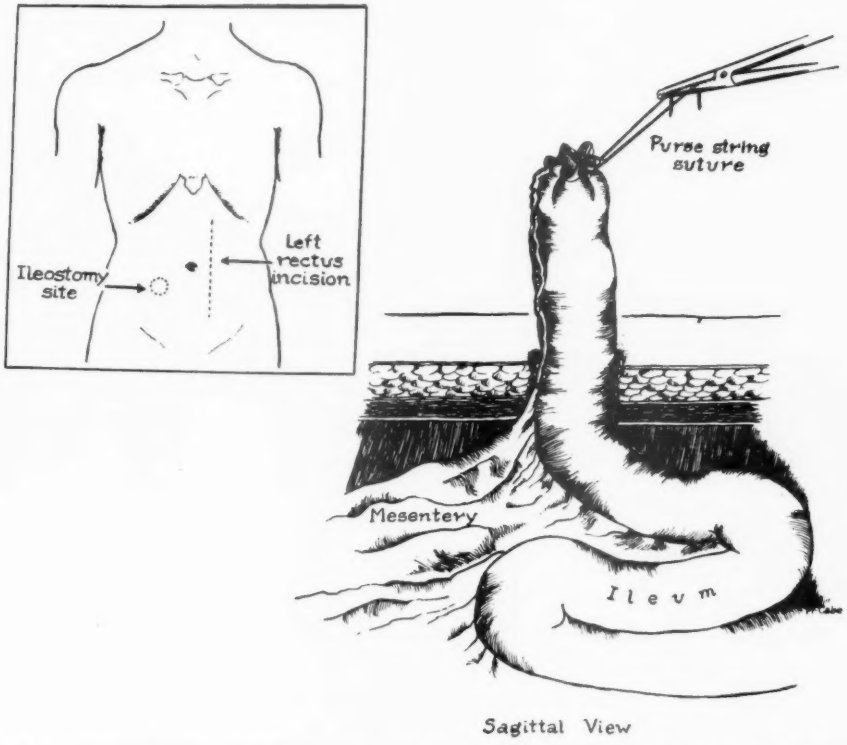

Fig. 1.—Diagrammatic sketch in sagittal view of operation of ileostomy showing the exteriorization of the permanent ileostomy limb through the selected site in the right lower quadrant. Inset shows the long left rectus incision and the site for the ileostomy.

The proximal ileostomy limb is now closed temporarily with Parker-Kerr stitch of silk, leaving the ends long. A clamp inserted into the abdomen through the opening made for the ileostomy site grasps the ends of the Parker-Kerr stitch and is withdrawn, pulling after it the inverted ileostomy loop in such a way as to have the cut-edge of the mesentery directed caudally. At this stage the limb of ileostomy should project 2½ to 3 inches beyond the skin surface (Fig. 1).

The next step in the operation consists of the fixation of the cut edge of the mesentery to the parietal peritoneum caudal to the emergence of the ileum from

the abdomen. About four sutures of silk suffice for this purpose. We are of the opinion that this maneuver alone has decreased markedly the incidence of ileostomy prolapse. In our group of 173 patients reported eighteen months ago, the prolapse incidence was 2 per cent, in marked contrast to that of 14 to

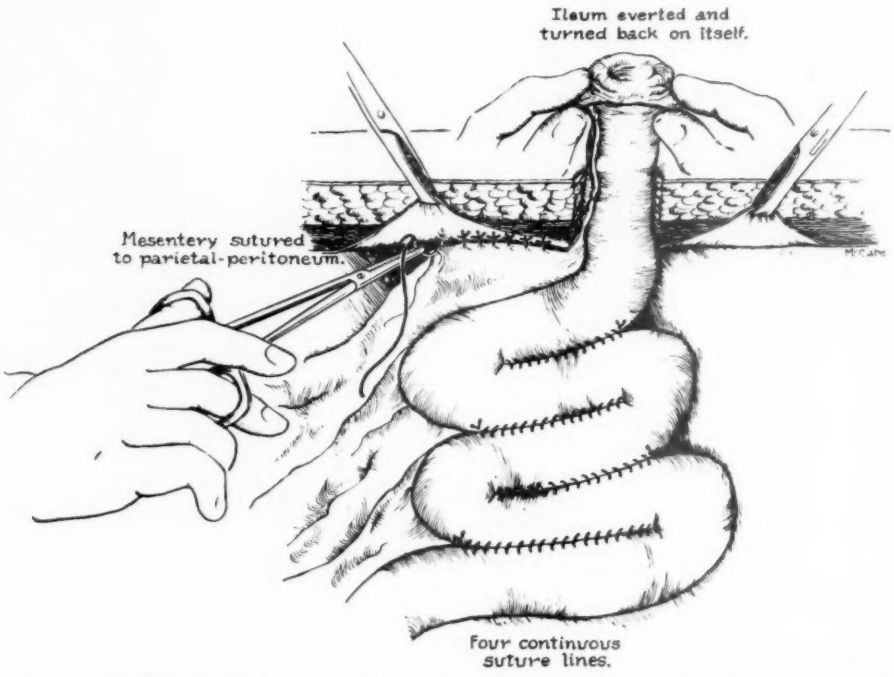

Fig. 2.—Drawing in sagittal view of the details of the operative procedure showing the fixation of the cut edge of the mesentery to the parietal peritoneum and the plication of the terminal 2 feet of ileum. The artist has indicated the beginning of the eversion of the ileostomy which is done at the completion of the operative procedure after abdomen is closed.

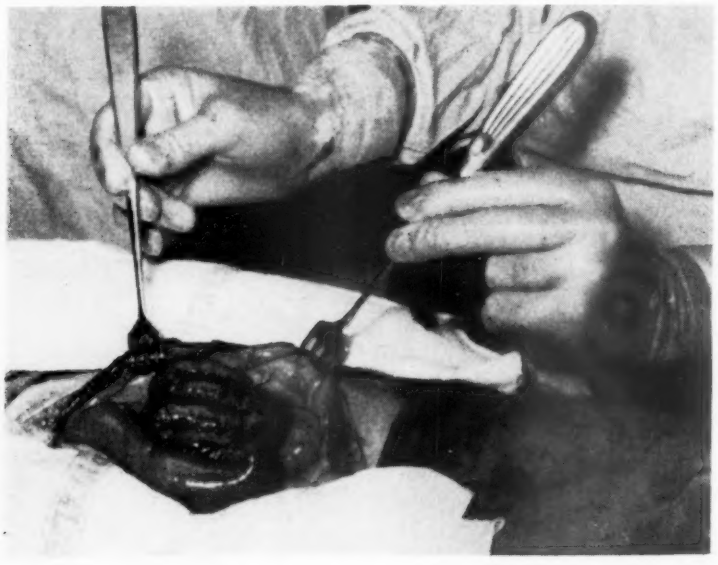

Fig. 3.—Photograph at operating table of the plicated terminal ileum. The abdominal wall has been lifted to demonstrate the sutured loops of bowel.

20 per cent reported in the literature. The third step in the fashioning of the ileostomy is the performance of a modified Noble plication of the terminal 18 to 24 inches of ileum. Beginning an inch or two from the emergence of the ileal limb from the abdomen, 2 loops of bowel approximately 6 inches each in length are approximated and sewn together with a continuous serosal suture of triple zero chromic catgut, the line of suture resting midway between the mesenteric and antimesenteric borders. The next proximal segment of ileum is then approximated to the preceding one and the procedure is repeated until 4 suture lines are completed (Figs. 2 and 3). In this manner the terminal 2 feet of ileum are placed in a definite position by the surgeon, thereby controlling this segment of bowel. The purpose of this maneuver is twofold: (1) to prevent partial obstruction within the abdomen, so frequently seen heretofore as one of the causes of ileostomy dysfunction, and (2) as an added factor in the prevention of ileostomy prolapse, as reported by Lichtenstein and Herzikoff.[18]

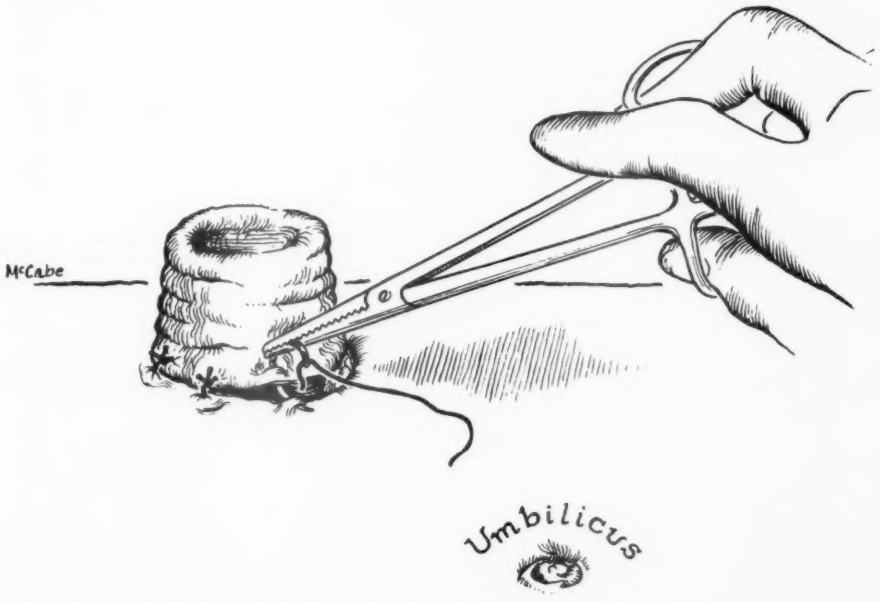

Fig. 4.—Drawing showing the details of the Brooke procedure of eversion of the full thickness of the terminal ileum with suture of its edge to the circular skin incision.

The left rectus incision is now closed and the final step in the construction of the ileostomy is carried out. The silk suture occluding the end of the exteriorized ileum is removed and the raw traumatized edge of bowel is excised. The full-thickness of ileum is now everted upon itself, the maneuver of Brooke,[4] and the distal edge is sutured to the circular skin incision. Eight stitches of fine chromic catgut will effect a firm closure (Figs. 4 and 5). We do not believe it is necessary or desirable to place sutures between the bowel wall and the fascia. It is to be noted that in every instance in our group of patients where the Brooke procedure was carried out, primary union between bowel edge and skin occurred, without infection, dead space, hematoma, or granulation tissue. A thin gauze dressing is now applied to the left rectus incision. The skin surround-

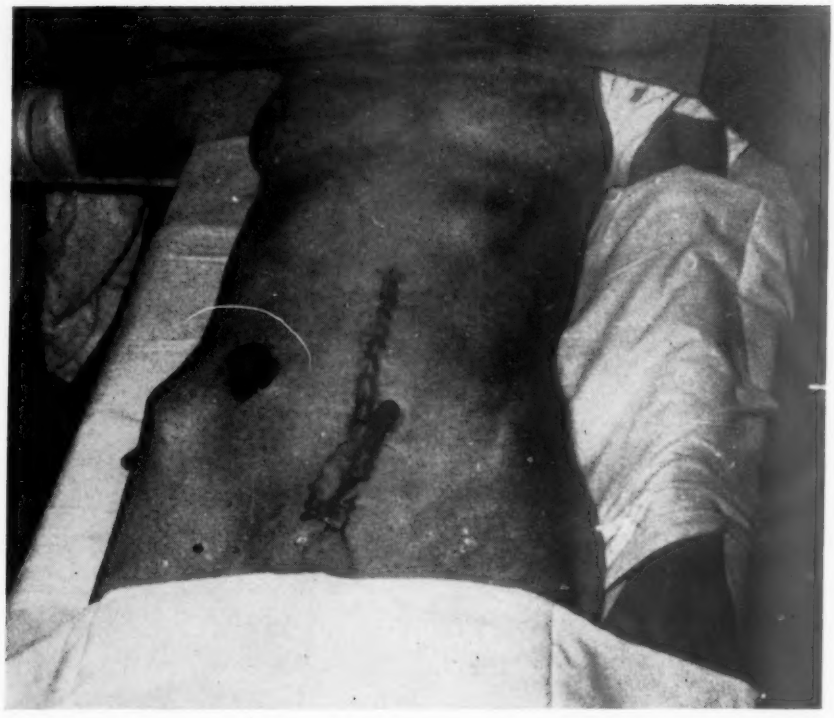

Fig. 5.—Photograph of patient at completion of operation showing newly formed ileostomy and the exteriorized distal sigmoid at the lower end of the left rectus incision.

Fig. 6.—Photograph of patient at completion of operation showing the immediate application of the temporary ileostomy bag.

ing the ileostomy is painted with tincture of benzoin and a temporary plastic Fazio ileostomy bag is immediately applied, after cutting a hole in the facing to match the size of the ileostomy end (Fig. 6). It will be seen that there is no longer any need for occluding clamps or intubation of the ileostomy which was formerly employed to prevent contamination. On the basis of our experience so far, we believe that the major complications of ileostomy such as skin excoriation, prolapse, dysfunction, wound separations, fistula and stenosis, so frequently encountered heretofore, have been all but eliminated by the operative regimen of circular excision of skin, fixation of the ileal mesentery, modified Noble plication of the terminal ileum, eversion of the bowel end, and immediate application of the temporary plastic bag.

Of course, it should be mentioned that, if a colectomy is to be done at the same time, the left rectus incision is lengthened and the step of exteriorization of the distal ileum is eliminated. Otherwise, the fashioning of the ileostomy is the same as described after the colon is removed. The distal sigmoid after excision of the colon is exteriorized through the lower end of the rectus incision. Berg, many years ago, emphasized the importance of this step of exteriorization of bowel in the surgical therapy of ulcerative colitis. There must always be an external vent for accumulated diseased bowel secretions.

EXPERIMENTAL OBSERVATIONS

In order to secure accurate observations on the effects of the modified Noble procedure recommended in this paper, a number of dogs were operated upon under the usual rigid aseptic precautions and numerous loops of bowel were sewn together by the technique described. Interrupted silk sutures were used in one instance, interrupted fine chromic catgut in another, continuous silk in a third, and continuous fine chromic in a fourth. The firmest union was obtained with continuous 3- or 4-0 chromic catgut, which was quite different from the stringy, segmental effect obtained with interrupted stitches. Reoperation was done at varying periods of time to note repair processes and the presence or absence of any degree of bowel obstruction. Gastrointestinal x-ray series were done in a few instances to note bowel position, any obstructive signs, and the rate of passage of barium through the agglutinated segments of intestine. The reparative processes have already been mentioned. In no instance was any evidence of obstruction noted. Figs. 7 and 8 indicate the gross appearance of the sutured loops of bowel 1½ weeks later and the stepladder appearance in the x-ray film after 3½ months. From observations in the experimental laboratory, it becomes clear that the modified Noble procedure described in the text results in firm union between the sutured loops of bowel and that no degree of bowel obstruction is produced thereby.

Numerous clinical observations at the operating table at the time of the final operation of abdominoperineal resection for the removal of the remaining sigmoid and rectum would seem to afford additional evidence for the need of the Noble plication procedure in the fashioning of the ileostomy. In a large group of patients operated upon prior to the adoption of our current regime, it was noted practically in every instance at the final operation, that the terminal

foot or two of ileum was coiled and fixed in varying positions by firm adhesions, apparently the result of a local peritonitis occurring after the ileostomy operation. Nature evidently intervened to supply her own defensive mechanism and fashioned a crude plication. By deliberately suturing together the terminal loops of ileum, the surgeon may now accurately fix the bowel in the position of choice.

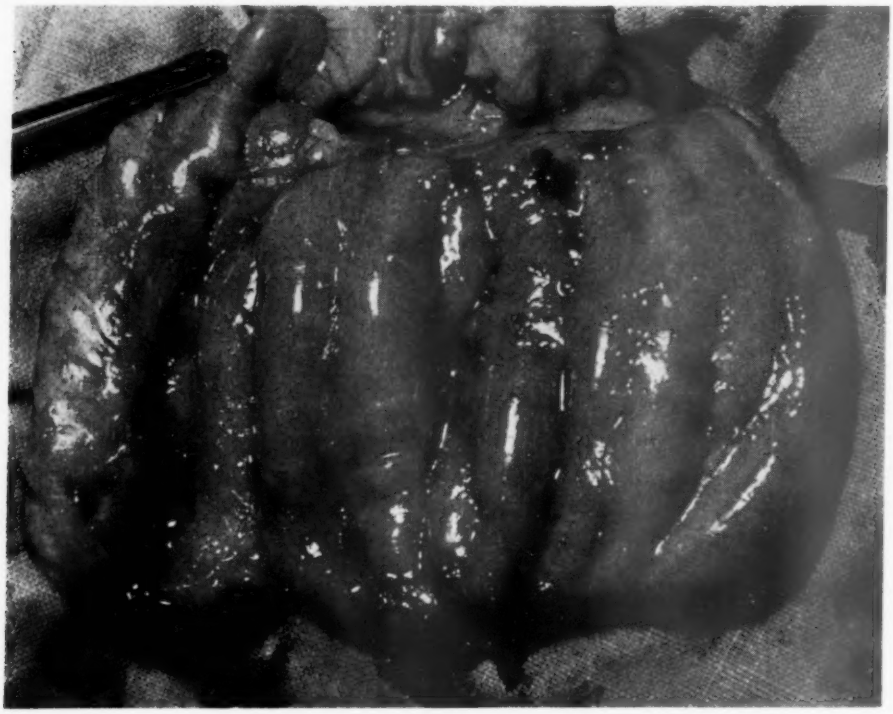

Fig. 7.—Photograph of the result of plication operation in a dog taken 10 days postoperative on re-exploration.

Discussion of this problem of ileostomy dysfunction would not be complete without reference to another cause of this difficulty which has no connection whatsoever with the ileostomy itself. We refer to the occurrence of partial intestinal obstruction produced by the fixation of a loop of ileum or jejunum to a part of the raw surface created by the removal of the colon. The clinical picture presented by this complication is almost identical with that already described in the early part of this paper and can occur, of course, after all the details of our operative regime have been scrupulously carried out. We would venture to predict that with the advent of the operation of ileostomy and subtotal colectomy in one stage and its more widespread use, there will be noted a mounting incidence of this particular complication. We must be concerned now with its recognition as a not infrequent occurrence and with the adoption of measures of prevention.

There are two schools of thought today concerning the question of reperitonealization after the operation of colectomy. One, probably the majority,

believes that it is not necessary to cover all raw surfaces, and the other feels strongly that every denuded area should be carefully covered with peritoneum to minimize the risk of late obstruction. In the early years of our experience with the surgical therapy of this disease, we did not practice reperitonealization and noted an alarming incidence of late intestinal obstruction with an attendant mortality of 40 per cent. We then completely revamped our technique and

Fig. 8.—X-ray film showing ingestion of barium in dog that had the plication operation of the entire small intestine 3 months prior showing a stepladder appearance and the absence of any obstruction.

began to practice careful peritonealization of both lumbar gutters, closure of the lesser sac by suturing the transverse mesocolon to the gastrocolic ligament in such a way as to bury all raw surfaces and ligated vessels, and elimination of peritoneal pockets. There was noted subsequently a gratifying decline in the incidence of intestinal obstruction. But, when we began doing colectomy for the acute fulminating phase of ulcerative colitis, it was felt that closing the lumbar gutters would invite postoperative complications because of the well-known permeation of the retrocolic areolar tissue with organisms derived from the acutely inflamed colon. We therefore left unclosed all raw surfaces following colectomy for acute disease, but continued careful reperitonealization in the interval chronic cases. In the last 9 cases of colectomy for acute disease, there have been 3 instances of partial intestinal obstruction producing the typical ileostomy dysfunction syndrome in the postoperative period and requiring reoperation for correction. The last case in this series is detailed below. As a result of this experience we have come to feel that careful peritonealization should be practiced in all cases and that provision should be made for drainage of each lumbar gutter through stab wounds in the flanks. It is felt that this technique supplemented by vigorous antibiotic therapy should result in a negligible incidence of flank infection and postoperative intestinal obstruction.

RESULTS OF RECOMMENDED OPERATION

It is now a little over a year since this operative regimen was instituted and 21 patients have been treated. The complications of skin excoriation, prolapse, wound separation, fistula, and stenosis have been singularly absent. There were 2 instances of possible ileostomy dysfunction. In one, a woman of 43, the ileostomy ceased functioning for twelve hours on the fifth day. Levin tube drainage of a distended stomach quickly relieved the suspected obstruction. It is doubtful that this represented an instance of true dysfunction. The second case was somewhat different. The patient, a boy of 14, was extremely ill at the time of operation which consisted of a one-stage subtotal colectomy and ileostomy. The preparatory preoperative period was prolonged and intensive. The ileostomy began to function twenty-four hours after operation. For the succeeding twenty-four days, there occurred periodic episodes of gastric retention, thin ileostomy discharge in large quantities, little fever, no abdominal cramps, and lassitude. The fluid losses both by ileostomy and kidneys were enormous. During one twenty-four-hour period it was necessary to replace 10,000 c.c. of fluid intravenously. Repeated scout films of the abdomen showed moderate diffuse dilatation of the entire small bowel and it was assumed that the clinical picture was due to a local peritonitis at the site of the plication. It was a grave error in judgment to defer operation so long. This was done on the twenty-seventh day after the original colectomy. A low grade hemorrhagic abscess was found in the left lumbar gutter near the spleen to which had become adherent a loop of proximal ileum producing a partial obstruction. The loop was freed and peritonealized and the retrocolic area drained through a left flank stab wound. The patient subsequently died of peritonitis. Among the 21 patients, 18 had a subtotal colectomy and ileostomy in one stage, and 3 had a revision of a previously made

ileostomy. There was one death and the remaining patients have remained well. In no instance has there been any subsequent ileostomy difficulty or intestinal obstruction (Figs. 9 and 10).

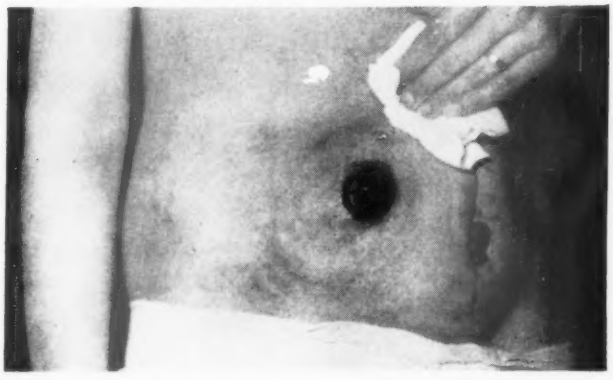

Fig. 9.—Photograph of patient taken on the tenth postoperative day showing the relative minimal swelling of the newly formed ileostomy and the exteriorized sigmoid at the lower end of the left rectus incision.

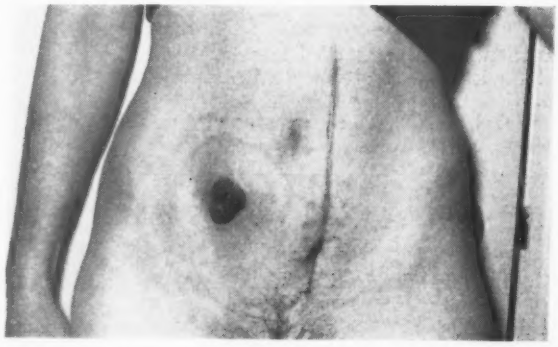

Fig. 10.—Photograph of patient taken 3 months after operation showing the final contraction of the ileum, absence of skin irritation and forward projection of the ileostomy stoma.

CONCLUSIONS

1. The operation of ileostomy for ulcerative colitis has always been associated with an abnormally high incidence of a variety of complications, of which the most important is "ileostomy dysfunction."

2. There is considerable evidence to substantiate the theory of Crile and Turnbull that ileostomy dysfunction is due to a serositis of the exteriorized segment of ileum.

3. It is our opinion that this serositis or localized peritonitis extends also within the abdomen to involve the terminal 18 to 24 inches of ileum.

4. To overcome practically all of the complications of ileostomy, an operative regimen is recommended which consists of a circular skin excision at the site of ileostomy, fixation of the mesentery to the parietal peritoneum, a modified Noble plication of the terminal 2 feet of ileum, eversion of the whole thickness of the exteriorized end of ileum by the method of Brooke, and the immediate application of a plastic bag.

5. Another cause of ileostomy dysfunction, unreleated to the ileostomy itself, is the development of a partial intestinal obstruction due to fixation of a loop of small bowel to the raw surface produced by the colectomy. The frequency of this complication is discussed and methods for its prevention are suggested.

6. In a series of 21 consecutive cases, there has been only one instance of dysfunction due to a partial obstruction in mid ileum and no skin excoriation, prolapse, wound separation, fistula, or stenosis. There was one death. The remaining patients have remained well.

ADDENDUM

Since this paper was submitted for publication, 11 additional patients were operated upon. There were no ileostomy complications or deaths.

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PELVIC EXENTERATION FOR CARCINOMA OF THE LOWER COLON

ALEXANDER BRUNSCHWIG, M.D., NEW YORK, N. Y.

(From the Memorial Center for Cancer and Allied Diseases)

CLINICAL observations have revealed that there is a rather wide variation in the course of malignant tumors and that this is related in some fashion to the organ of origin and histogenesis of the particular neoplasm in question as well as to unknown factors now sometimes referred to as host resistance. Examples of this are the differences in the usual clinical course observed in carcinoma of the head of the pancreas, extrabiliary bile ducts, stomach, colon, prostate, urinary bladder, esophagus, lymphoblastoma, and so forth.

Carcinoma of the lower colon, in particular, would appear to exhibit a relatively slower course than carcinomas of some of the other abdominal viscera. Not infrequently it manifests local invasive characteristics prior to giving rise to widespread metastases. Thus, it may resemble carcinoma of the cervix. For this reason patients with locally invasive lower colon cancer and no macroscopic spread out of the pelvis may be considered candidates for total pelvic exenteration, should the bladder, prostate, or uterus, vagina, and bladder be invaded.

Such candidates are usually men because in women the vagina and uterus, interposed as they are between colon and bladder, constitute an effective barrier to forward spread of the colonic lesion into the urinary bladder. However, in women, pelvic spread of primary colon cancer may be such that total pelvic exenteration may become necessary to encompass the lesion.

Pelvic exenteration with wet colostomy in the female for gynecologic cancer was first performed by the writer in December, 1946, and the first series of these operations was published in 1948.[2] An integral part of the operation is the thorough pelvic lymph node excision and denudation of the pelvic walls of all lymph nodes and fatty tissues with denudation of the sacral plexus and resection of both hypogastric artery and vein. The only structures remaining in the pelvis are the external iliac arteries and veins, obturator nerves, and trunks of the sacral plexus.

In 1950, Appleby[1] published a series of 6 male patients in whom he had carried out the procedure which he referred to as proctocystectomy. Four were alive and well between four and one-half to seven years later. One lived fourteen months and one was an operative death. In his report, no mention is made of an associated thorough pelvic lymph node excision.

Among a series of over 350 pelvic exenterations (anterior and total) carried out in my private and ward service for advanced pelvic cancer, the large

The secretarial work for this study was made possible by a grant from Mr. James Adams of New York City.

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TABLE I

PATIENT, SEX, AND AGE (YEARS)	PREVIOUS HISTORY (ELSEWHERE)	OPERATION	PATHOLOGY	ULTIMATE COURSE
1. M. P. M.; 46	Feb., 1947, colostomy for inoperable carcinoma sigmoid	1/16/48. Total pelvic exenteration with resection of 32 cm. of ileum, rt. ureter implanted into cecum and lt. ureter into sigmoid; wet colostomy	Adenocarcinoma of sigmoid fungating into bladder and metastasis to mesenteric node; invasion of ileum	Effective palliation, returned to full activities for many months; recurrences developed throughout abdomen; severe attack of pyelitis; died 22 months after exenteration of recurrences
2. J. B. M.; 50	Sept., 1949, loop colostomy for inoperable carcinoma of sigmoid	12/8/49. Total pelvic exenteration; wet colostomy. 4/20/50, 5/20/50, 6/2/50 revisions of colostomy and transfer of both ureters to skin ureterostomies	Adenocarcinoma of rectal colon with extension into bladder wall	Clinical status excellent since final colostomy revisions and cutaneous ureterostomies; living and free from evidence of disease 6 years after operation
3. S. G. F.; 51	Aug., 1949, exploratory laparotomy and segmental resection of colon for adenocarcinoma	10/25/49. Total pelvic exenteration and resection of segment of terminal ileum; wet colostomy	Adenocarcinoma of rectum with spread into uterus and segment of ileum; metastatic to mesenteric nodes; bladder not involved	Died 5 months after operation of widespread metastases
4. P. M. M.; 60	No previous operations; rectal bleeding, 4 months	9/18/51. Total pelvic exenteration; wet colostomy	Adenocarcinoma of rectal colon with invasion of rectovesical septum; pelvic lymph nodes negative	Living and well 4 years and 1 month after operation; at age 64 has returned to work as carpenter; two attacks of pyelitis in 4 years
5. E. W. F.; 59	Bleeding from rectum; anterior resection of rectal tumor 2 years previously	7/10/52. Total pelvic exenteration with en masse resection of lower half of sacrum	Adenocarcinoma of rectum with metastases to cervix, vaginal wall, serosa of right tube, right ureter, left hypogastric and obturator nodes; invasion of presacral tissues by carcinoma	Patient died on 19th postoperative day; necropsy not obtained; cause of death, peritonitis (?)
6. J. R. M.; 43	Colostomy 3 months previously for inoperable cancer of rectum	8/19/52. Total pelvic exenteration; cutaneous ureterostomies	Adenocarcinoma of rectum invading lymphatics of outer wall of bladder; negative pelvic lymph nodes	Returned to full activities; continues to be clinically well; has two asymptomatic tumor masses in lower anterior abdominal wall that are slowly growing 3 years 2 mo. after operation
7. G. S.	Colostomy 2 years previously	11/4/52. Total pelvic ex-	Adenocarcinoma of rectum in-	Died of recurrences 15 months

7. G. S. F.; 31	Colostomy 2 years previously for inoperable cancer of colon	11/4/52. Total pelvic exenteration	Adenocarcinoma of rectum invading rectovaginal septum, cervix, left parametrium, left ovary; metastases to perirectal and right hypogastric lymph nodes and lower vaginal mucosa; rectovaginal fistula; chronic cystitis; metastasis to left external iliac node	Died of recurrences 15 months after operation; satisfactory palliation during lifetime
8. R. Y. F.; 51	Left nephrectomy 5/22/52; abdominoperineal resection 8/11/52	11/7/52. Total pelvic exenteration, resection part of sacrum, right cutaneous ureterostomy	Adenocarcinoma involving posterior vaginal wall	Died of recurrence 16 months after exenteration; had prefrontal lobotomy few months before death
9. J. H. M.; 44	Exploratory laparotomy 2 months previously for inoperable carcinoma of rectal colon	12/22/52. Total pelvic exenteration; wet colostomy	Adenocarcinoma of rectum extending through wall of colon into cul-de-sac; all lymph nodes negative	Died 3 months after operation at another hospital, had small bowel fistula; necropsy revealed no evidence of residual cancer
10. M. C. M.; 41	Abdominoperineal resection for carcinoma of colon 8 years previously	5/18/53. Anterior pelvic exenteration, i.e., total cystectomy, resection of tissues in hollow of sacrum, prostatectomy, pelvic node excision, resection of perineal floor, ileal bladder, resection of inferior margins of pubic arch	Gelatinous adenocarcinoma consistent with bowel origin and extending through wall of bladder into prostate gland; lymph nodes negative	Living and well without evidence of disease 2 years 5 months after operation
11. M. H. F.; 39	Previous radiation therapy to pelvis	2/16/54. Total pelvic exenteration with bilateral cutaneous ureterostomies	Adenocarcinoma of sigmoid with focal areas of epidermoid metaplasia extending into posterior wall of bladder with large fistulous tract and into anterior wall of uterus; metastatic to nodes of sigmoid, rectal mesentery and right ovary	Died at home 2 months after operation
12. C. C. M.; 56	Previous exploratory laparotomy only for inoperable cancer of colon	10/7/54. Total pelvic exenteration; wet colostomy; intense pelvic inflammation	Adenocarcinoma of rectum; bladder is not involved but adjacent to it is purulent exudate; nodes negative but at level III is a small nodule of metastatic tumor; Dukes C	Living and well 1 year 2 months after operation; fully active

majority for cancer primary in the cervix, there were twelve instances of primary carcinoma in the lower colon. Seven of these were in men and five were in women.

The purpose of this report is to record the experiences with total pelvic exenteration for lower colon cancer. Surgeons doing this work should record such experiences in order that some impression can be gained as rapidly as possible concerning the possibilities of the operation for rectal cancer since evidence is at hand to indicate that it is an established procedure for advanced cancer of the cervix.

TECHNIQUE

In essential detail the technique does not differ from the operation described for women. In certain respects it is more easily carried out in men than in women since the mass of tissue to be resected is less extensive, there being only rectum, bladder, and prostate, whereas in the female there are also the uterus, vagina, and adnexae to be removed. On the other hand, the more restricted space of the male pelvis renders stripping of lymph node and pelvic wall fatty tissues more difficult.

The author's technique has been previously described for both male and female.[3, 4]

The problem of lower urinary tract diversion has been met by the wet colostomy. While some objections to this have been raised by others, it still remains satisfactory in my hands. However, other measures have been resorted to, such as skin ureterostomies (when necessity has demanded this). The possibilities of the ileal bladder are also being explored; in one of these cases an ileal bladder was constructed.

RESULTS

The patients' histories are summarized in Table I. It is apparent that the results in men are better than in women.

A summary of the 7 male patients reveals:

1 living and well, 6 years
1 living and well, 4 years 2 months
1 living and well, 3 years 3 months (has asymptomatic recurrent nodules in abdominal wall)
1 living and well, 2 years 6 months
1 living and well, 1 year 2 months
1 lived, 1 year 10 months (effective palliation); died of cancer
1 lived, 3 months; cause of death (in another hospital) ileal fistula, no carcinoma at necropsy
Hospital mortality: 0.

A summary of the 5 female patients:

1 lived, 1 year 3 months; died of recurrences
1 lived, 1 year 4 months; died of recurrences
1 lived, 5 months; died of recurrences
1 lived, 2 months; died at home (cause ?)
1 surgical mortality (nineteenth day)
Hospital mortality: 1 patient.
Total hospital mortality (men and women): 1 patient, 8 per cent of series.

In 3 patients, one man and 2 women, the extent of disease was such that portions of the bony pelvis were excised with hammer and chisel along with the pelvic soft parts. In the male patient, the inferior margin of the pubic arch

was excised and the patient remains well without evidence of recurrence one year and five months after operation. In the two women, a portion to one-half of the lower sacrum was excised; the latter was a surgical mortality (nineteenth day, but not due to excision of part of the sacrum) and the former lived for a year and four months, and died of recurrences.

An explanation for the better results in men is that the close proximity of bladder to rectal colon renders total exenteration mandatory earlier in the course of the spread than in women where the interposition of uterus, parametria, and vagina between bladder and rectum, constitutes a barrier to bladder invasion and therefore by the time the bladder seems implicated, the disease has become relatively farther advanced when total exenteration is indicated. In women, when rectal cancer has spread forward to involve uterus and/or vagina, a posterior exenteration, i.e., en masse resection of pelvic colon, uterus, and vagina suffices. This is a situation more comparable to that in men indicating "total exenteration."

SUMMARY

Total pelvic exenteration for carcinoma of the rectum was performed in 7 men and 5 women. The results in men certainly warrant the continued performance of this operation. In women, the results in 5 patients left much to be desired, but 2 of the 5 patients had to have portions of the sacrum resected.

The reasons for better results in men than in women are discussed. This is a limited series but by no means contraindicates further exploration of the possibilities of total pelvic exenteration in women for rectal cancer seemingly involving all pelvic viscera.

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STRANGULATED DIAPHRAGMATIC HERNIA WITH GANGRENE AND PERFORATION OF STOMACH

G. H. C. JOYNT, M.D., TORONTO, ONTARIO

(From the Toronto Western Hospital and the Department of Surgery, University of Toronto Medical School)

STRANGULATED diaphragmatic hernia is relatively uncommon and the diagnosis should be considered in all cases of obscure lower thoracic or upper abdominal pain. The treatment is prompt surgical therapy with replacement of the abdominal contents and repair of the defect in the diaphragm. The association of gangrene and perforation of the stomach with strangulated diaphragmatic hernia is rarely encountered in surgical literature and, in this group, the mortality rate is high. The following case report illustrates the difficulty in diagnosis and the resultant complications which may develop.

CASE REPORT

The patient, a 41-year-old man, was admitted to the Toronto Western Hospital on the evening of Dec. 5, 1951, as an acute abdominal emergency. He gave a history of onset of sudden, severe, crampy abdominal pain starting about 10 A.M. and lasting about thirty minutes. This was followed by a dull, persistent, nonradiating pain in the epigastrium which produced nausea and vomiting. His past history indicated a proved duodenal ulcer, in 1947, with intermittent symptoms up to the time of admission.

Physical examination revealed a fairly well-nourished man who appeared seriously ill. There was generalized abdominal tenderness with rigidity in the upper abdomen. The abdomen was not distended and no peristaltic sounds were present. The chest was reported as negative and the white blood count was 22,700 per cubic millimeter, with urinalysis normal.

A provisional diagnosis of perforated peptic ulcer was made and the abdomen was explored under general anesthesia. A scarred, healed ulcer was noted in the first portion of the duodenum but no perforation was found. The stomach was palpated, inspected, and appeared normal. The lesser sac was opened but no sign of peritonitis was observed.

On the first postoperative day the patient felt greatly improved with normal temperature and pulse, but the following day his temperature rose to 100° F., with pulse rate of 120 per minute. At this time, examination of the chest revealed dullness with absent breath sounds in the left lower chest and a roentgenogram of the chest showed a massive homogeneous density occupying the lower two-thirds of the left lung field, which was reported as pleural effusion (Fig. 1). Thoracentesis was carried out and this yielded about 300 c.c. of thin, reddish fluid with a hemoglobin content of 30 per cent. After the aspiration was performed (Fig. 2), questionable bowel sounds were heard in the lower lung field and a barium swallow showed the stomach to be within the pleural cavity (Fig. 3).

On Dec. 24, 1951, thoracotomy was carried out by resecting the ninth left rib. When the pleural cavity was entered a good deal of stomach content and yellowish fibrinous-flecked fluid was evacuated. A gangrenous necrotic mass with two sites of gross perforation occupied the lower portion of the left thoracic cavity with the lower lobe of the left

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Fig. 1.

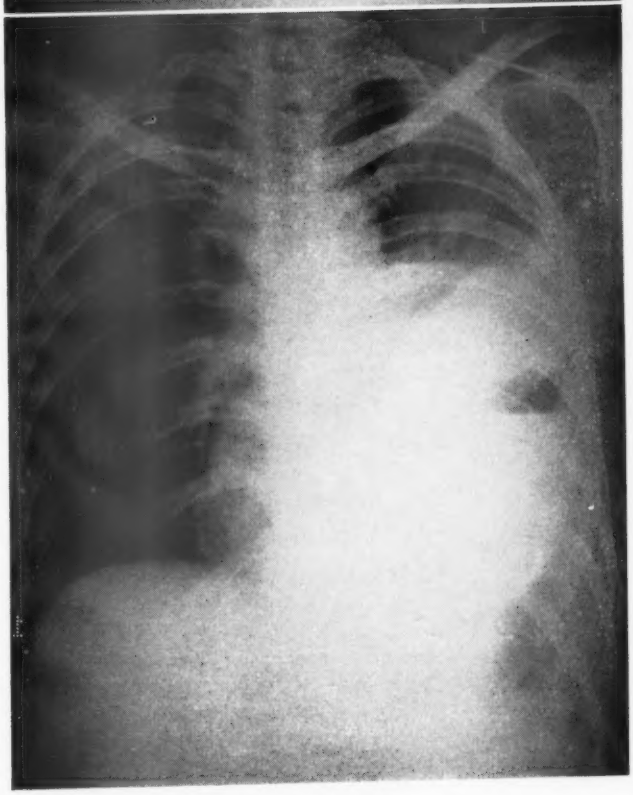

Fig. 2.

lung atelectatic and compressed upward. Fig. 4 presents a diagrammatic sketch of the hernia and gangrenous stomach. The mass in the chest was freed by blunt dissection, and the margin of the diaphragm which represented the constricting ring of the diaphragmatic hernia, 4 cm. in diameter, was enlarged and freed throughout its circumference. The hernia was the traumatic type with no definite sac and was located in the dome and posterior half

Fig. 3.

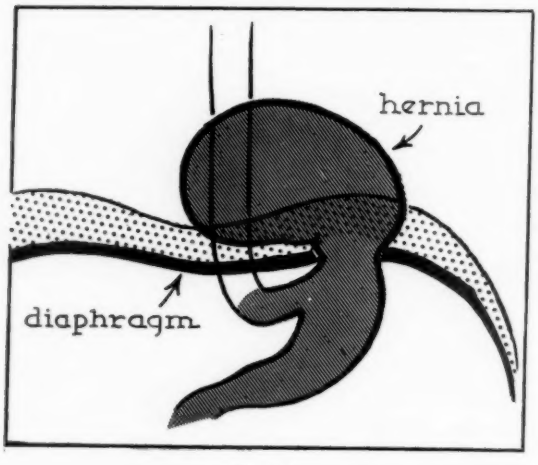

Fig. 4.

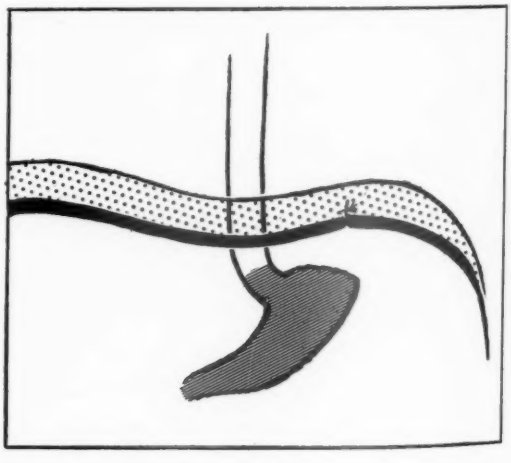

Fig. 5.

of the diaphragm. A thoracoabdominal incision was made and resection of the extensive gangrenous portion of the fundus and body of the stomach was carried out and the defect in the diaphragm was repaired (Fig. 5). Attempts at expanding the lower lobe were ineffectual and the peel on the visceral pleura was not mature enough for decortication.

Fig. 6.

Fig. 7.

As a result, closed drainage was established in the lower left pleural cavity in an attempt to obliterate the empyema pocket. Postoperatively, the patient had a moderately stormy course for a week but this gradually subsided with the development of a small empyema at the left base which was treated with repeated aspirations and the instillation of Varidase. He was discharged from the hospital on Jan. 27, 1952, but subsequently was readmitted in May, 1952, with a small left empyema cavity which was adequately controlled with a small limited thoracoplasty (Fig. 6).

A recent report from the patient indicates he has been working steadily as a service station attendant. He has slight discomfort in the region of the thoracoplasty scar but has had no recurrence of abdominal symptoms. Because of the extensive gastric resection, his meals of necessity are small and frequent but his nutrition is good. Fig. 7 represents a barium examination of the upper gastrointestinal tract two years postoperatively.

COMMENT

Postoperatively, the patient's past history was reviewed in detail. The only traumatic incident was a car accident in January, 1951, approximately one year previous to his admission to the Toronto Western Hospital, in which he had suffered a severe fracture of the left elbow which was treated in a shoulder spica. The hospital report at that time revealed no history of abdominal or thoracic trauma. A photograph which the patient produced showed a bent steering wheel. It was finally established that the patient had been thrown against the steering wheel, probably striking his upper abdomen. He recalled that he had some upper abdominal pain following the application of the shoulder spica but this was relieved when a window was cut in the cast over the epigastrium.

On the morning of his admission to the Toronto Western Hospital, the patient had shoveled some heavy, wet snow for ten to fifteen minutes. He felt tired and, after resting for about thirty minutes, suddenly developed severe upper abdominal pain. In view of his previous history of duodenal ulcer, the diagnosis on admission to the Toronto Western Hospital was perforated peptic ulcer. In retrospect, it would appear that the traumatic diaphragmatic hernia occurred at the time of the car accident one year previously and the heavy exertion on the morning of admission precipitated incarceration of the stomach.

DISCUSSION

Carter and Giuseffi have emphasized the importance of history and physical examination in the diagnosis of strangulated diaphragmatic hernia. In their review of 43 cases, in 1948, they noted that 85 per cent were of traumatic origin, the acute attack being precipitated by a relatively sudden increase in intra-abdominal pressure which usually occurred within three years of the injury. Pearson in his review of 31 cases, in 1953, reported about 60 per cent to be traumatic in origin. Gangrene of the stomach associated with diaphragmatic hernia is rarely encountered in the surgical literature. Hughes and associates, in 1955, collected 9 cases from the literature and reported one of their own. In this group of 10 patients, 2 survived gastric resection.

The physical signs in strangulated diaphragmatic hernia can often be misleading. The significant signs are usually referred to the left chest with dis-

placement of the mediastinum to the right with dullness or tympany in the lower portion of the thorax. Aspiration of bloody fluid from the left pleural cavity is an important sign and roentgenographic examination aids in establishing the diagnosis, particularly with evidence of a high left diaphragm and fluid in the left chest. When the stomach alone is strangulated, there are signs of acute gastrointestinal obstruction with absence of abdominal distention, and the presence of extraneous bowel sounds in the chest is an important diagnostic sign.

SUMMARY

Strangulated diaphragmatic hernia with gangrene of the stomach is relatively rare. Two patients who survived gastric resection have been reported in the literature. The patient just reported is alive and well four years following an extensive gastrectomy. Treatment is immediate surgery with resection of the stomach and repair of the hernial defect. A combined thoracoabdominal incision is recommended in order to cope with the herniated viscera which often adhere to the lung, thoracic wall, or diaphragmatic ring and also to deal with the possible flooding of the pleural cavity by stomach contents.

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FREE PERITONEAL GRAFTS AND NYLON SURFACING OF RESECTED LIVER WOUNDS

ABDOL H. ISLAMI, M.D., AND GEORGE T. PACK, M.D., NEW YORK, N. Y.

(From the Memorial Cancer Center)

IN EARLIER years when total left hepatic lobectomies were performed, and more recently when the more formidable right hepatic lobectomies were performed, the management of the interlobar transections sometimes proved to be troublesome due to the problems of hemostasis and closure of minute biliary fistulas. These lobectomies both left and right are always preceded by preliminary dissection of the porta hepatis with identification, isolation ligature and severance of the left or right branches of the hepatic bile duct, the hepatic artery, and the portal vein, which makes the procedure relatively safe. The liver is essentially a bipartate organ as far as the lobar arterial supply is concerned as there is little if any arterial intercommunication across the interlobar septum, but a recurrent branch of the complex left portal vein traverses the septum to empty its blood into the quadrate and caudate lobes. Awareness of the presence of this large venous trunk enables the operator to ligate it by purse string suture without considerable loss of blood. The preliminary placement of interlocking strangulating heavy sutures before transecting the septum conserves much blood. The medial cut surface of the remaining lobe is covered in part at least by as much of the falciform ligament as can be left attached to the superior surface of the liver. This is accomplished by cutting the falciform ligament away from the anterior abdominal parietes and diaphragm. It is then folded down and sutured snugly over the raw cut surface of the septum. In some instances it can completely cover the transected surface.

At times the dimensions of the falciform ligament are too small or the ligament is necessarily resected, as when involved by the cancer. The employment of absorbable gelatin sponges or oxidized cellulose as substitute coverings has not been equally satisfactory in our experience, although their temporary aid as hemostatic splints has been proven and is admitted.

Masters, Georgiade, Horton and Pickrell[9] have recently utilized the known ability of split-thickness skin grafts to serve hemostatically when applied to bleeding surfaces, by using this covering for denuded liver areas in dogs. In fifteen dogs they applied the split-thickness grafts to the transected middle lobe of the liver. Re-exploration was done two weeks later and the grafts were all found to have successfully taken. One to four months later the dogs were killed by exsanguination and the skin grafts on the liver inspected. All

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grafts remained intact, but had markedly contracted to 30 per cent of their original size. Small cysts containing a squamous cellular detritus were found where the graft overlapped the parietal peritoneum or liver capsule.

In humans we have never employed split-thickness skin grafts on the liver but we have successfully used free omental grafts and free peritoneal grafts from the abdominal parietes. One can safely denude a large segment of the abdominal wall of its peritoneal lining because it rapidly regenerates and often with few and uncomplicating adhesions. The employment of such free peritoneal grafts as hemostatic coverings for liver wounds follows not only the major lobectomies but also metastasectomies which are being done with increasing frequency. It is believed to lessen the quantity of postoperative bile drainage from the liver wound.

In order to study the end results of peritoneal grafting and the use of nylon sheets for the same purpose, a series of experiments was done utilizing dogs.

EXPERIMENTAL DATA

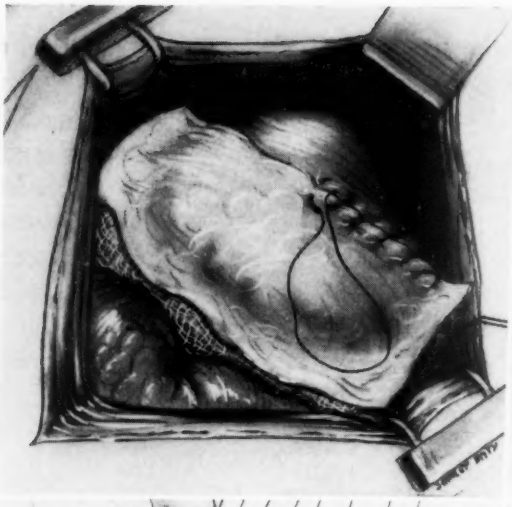
Ten mongrel dogs, male and female, in good health and weighing 9 to 12 Kg. were chosen. Food was withheld preoperatively for eighteen hours. The dogs were anesthetized by Pentothal sodium intravenously (35 mg. per Kg. body weight). The dogs were divided into two groups of five each.

Group I dogs were placed in the right lateral decubitus position and their abdomens opened through a right subcostal incision. A segment of peritoneum measuring 7 by 4 cm. was dissected from the left lateral wall of the abdomen. The left lateral lobe of the liver was chosen for resection and grafting. The peritoneal graft was sutured to the superior surface of the liver one centimeter proximal to the margin to be resected using a continuous locked stitch of 5-0 silk. The liver was transected one-half centimeter from the suture line. There was only slight oozing due to the preliminary placement of a proximal rubber-shod clamp. The free border of the peritoneal graft was next laid horizontally across the transected liver and sutured 0.5 cm. from the edge to the inferior surface. The occlusive soft clamp was later removed; the peritoneal graft ballooned slightly but was effective in controlling hemorrhage.

Group II dogs were operated upon through thoracoabdominal incisions and under intratracheal anesthesia. In these animals the liver pedicles were not clamped for hemostasis. In each dog two lobes were resected, the right and left lateral lobes. The cut surface of the left lateral lobe was covered with sterile nylon cloth and to the cut surface of the right lateral lobe was applied a free peritoneal graft. Interlocking deep mattress sutures of No. 1 plain catgut were inserted proximally to control bleeding. The peritoneal grafts and nylon coverings were sutured over the cut surfaces of the liver by the method previously described. There were no postoperative complications, hemorrhage or fatality.

The animals were explored for the second time at intervals of one to three months after the liver resection and grafting. The peritoneal grafts in all ten animals were successful with no evidence of hemorrhage or peritonitis. In only

Fig. 1.



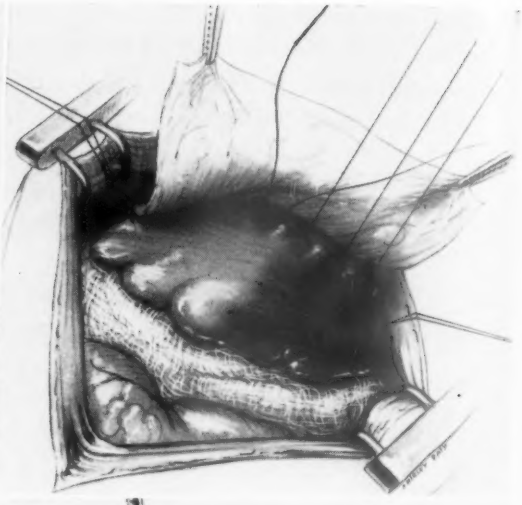


Fig. 2.

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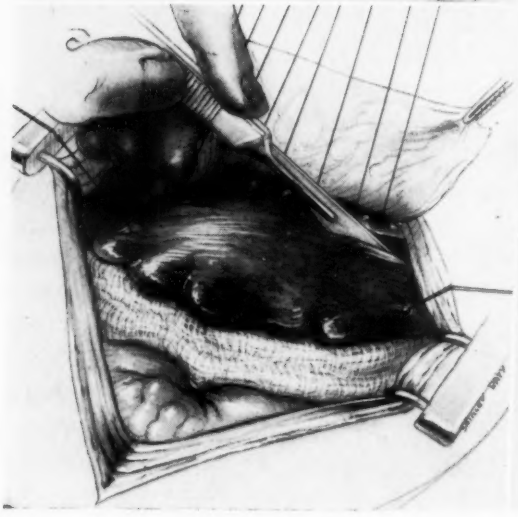

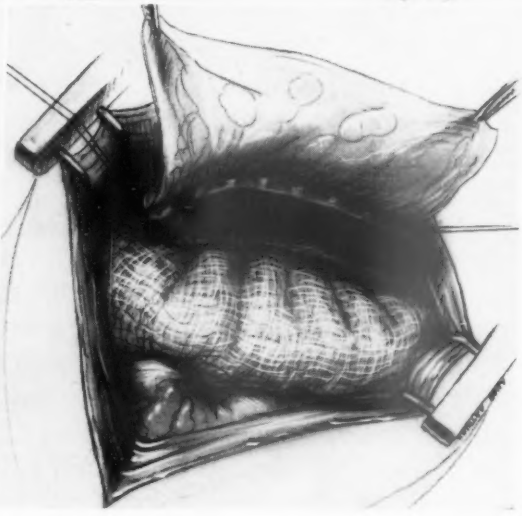

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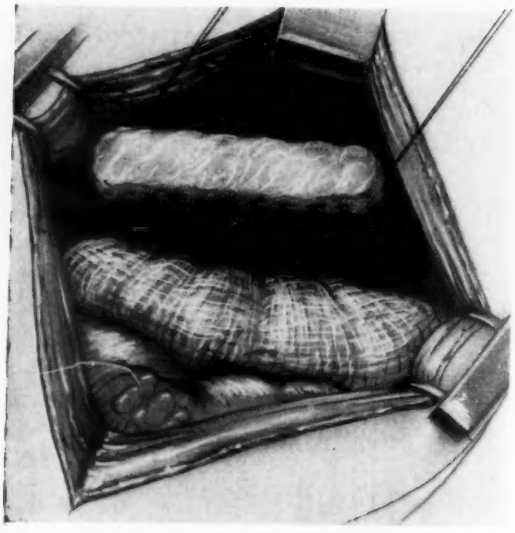

Fig. 1.—Free peritoneal graft sutured to superior surface of liver. First step.

Fig. 2.—Free peritoneal graft sutured to superior surface of liver. Preliminary mattress sutures inserted. The segment of liver lobule becomes darker as the sutures are tied.

Fig. 3.—Resection of the liver segment after the mattress sutures have been applied.

Fig. 4.—The lobule of the liver has been transected. The peritoneal graft previously attached on the superior side is now ready to be applied over the cut liver surface.

Fig. 5.—Free peritoneal graft completely sutured over base of transected left lateral lobe.

Fig. 6.

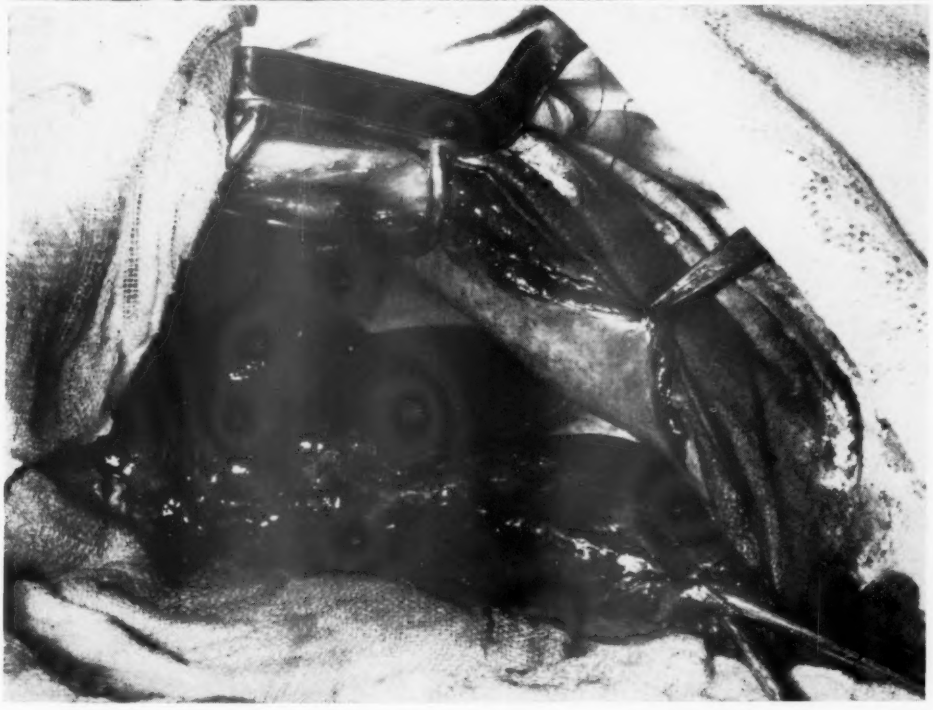

Fig. 7.

Fig. 6.—Two months after free peritoneal graft was applied to transected left lateral lobe of liver. Note freedom of contracture and absence of adhesions.

Fig. 7.—Nylon graft on raw surface of liver two months after partial hepatectomy showing wrinkling and contraction of nylon mesh.

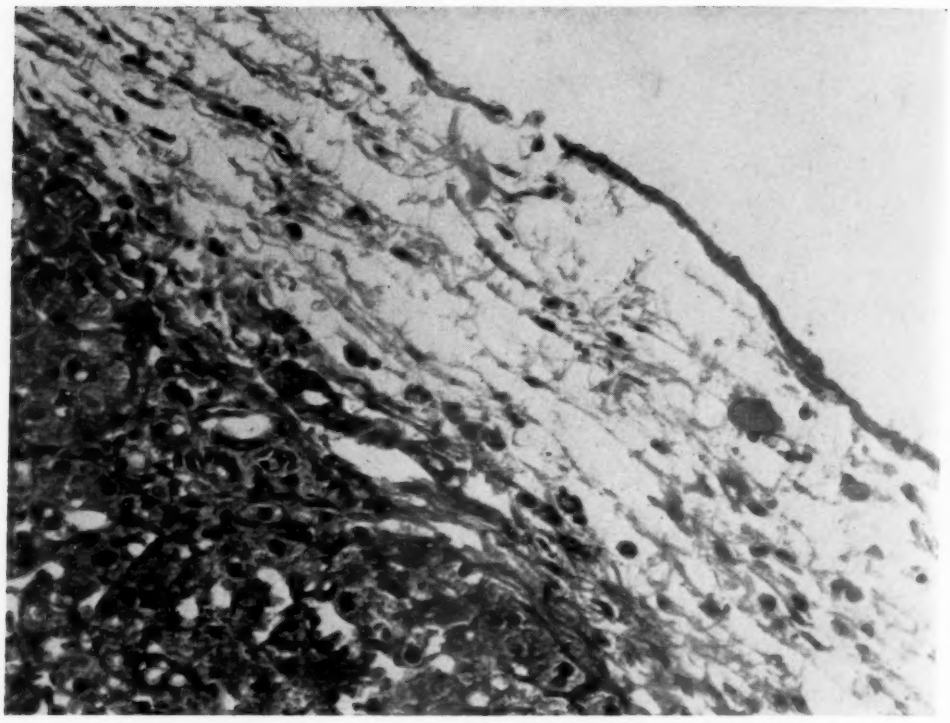

Fig. 8.—Liver surface at site of partial hepatectomy covered by a successful free peritoneal transplant two months before. Note the loose connective tissue of the peritoneum overlying the hepatic parenchyma (×273).

Fig. 9.—Liver surface at site of partial hepatectomy covered by nylon mesh. Individual nylon fibers are seen as rimmed oval clear spaces symmetrically spaced. Note focus of old hemorrhage immediately overlying the hepatic parenchyma. The connective tissue beneath, overlying and infiltrating the nylon mesh is dense and fibrous (×100; reduced ⅙).

one of the ten dogs was there an adhesion between the peritoneal graft and the intestine. In the instances of the nylon grafts there were adhesions in every case between the nylon and adjacent viscera but there was no sign of secondary bleeding. The nylon was adherent to the cut liver surface but there was considerable kinking and contraction with cyst formation.

The liver beds containing the peritoneal and the nylon grafts in all ten animals were resected for microscopical study. Under the microscope the peritoneal graft almost simulated the normal capsule of Glisson; a loose connective tissue layer intervened between the peritoneal covering and the subjacent normal hepatic parenchyma. The nylon grafts on the other hand were associated with a dense fibrous scar which infiltrated and overlaid the nylon mesh. Discrete foci of old hemorrhage were constantly seen immediately overlying the hepatic parenchyma.

CONCLUSION

Free peritoneal grafts from the abdominal parietes furnish a most satisfactory means of covering a cut liver surface. They act as a hemostatic covering and heal without contractures or adhesions. For this purpose, nylon is a poor substitute and is not recommended.

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THE USE OF COMBINED TUBES IN BILIARY TRACT SURGERY

ARMANDO NÚÑEZ NÚÑEZ, M.D., GUSTAVO VÁZQUEZ ROSALES, M.D., AND
JUAN RODRÍGUEZ IÑIGO, M.D., HAVANA, CUBA

(From the Surgical Department, University Hospital, Havana University)

EXPLORATION of the extrahepatic biliary passages is a surgical procedure which has been increasingly employed during the past twenty-five years, as evidenced by the statistics published in contemporary medical literature. Catell,[4] in 1929, indicated a proportion of 15 per cent of explorations of the biliary passages in patients operated on for cholelithiasis in the Lahey Clinic, and in 1947, Adams[1] at the same clinic and under the same circumstances, reported a ratio of 45.7 per cent.

Although some authors, such as Edwards,[8] perform a primary suture without drainage of the common duct, yet, the great majority of surgeons are in agreement that, after having been opened, this duct must be drained by some kind of rubber tube. Robson[10] of England, in 1902, was the first to drain the common duct, utilizing for this purpose an ordinary rubber tube directed upwards. Later the T tube was designed in order to facilitate the passage of bile into the duodenum. This tube is known as the Kehr tube although, in medical literature, it was first referred to by Deaver[7] in 1904.

The T tube has undergone various modifications. Catell,[5] in 1946, described a new type of T tube with one long horizontal arm passing through the papilla and leading to the duodenum. Baker[2] in 1941, designed a tube with one of the horizontal arms forming an angle of 135 degrees with the longitudinal portion in order to facilitate medical treatment in case of residual calculi. Best,[3] in 1950, modified the Baker tube using a double lumen in the vertical portion and also in the horizontal arm leading to the distal choledochus.

In order that the exploration of the biliary passages may be thorough and the relief of symptoms assured it is of primary importance to make sure of the permeability of Oddi's sphincter and of Vater's papilla by carrying out a dilatation of this structure or a papillotomy in case of necessity. Bakes' dilators will inform us of the initial diameter and of the final one obtained by the dilatation. At times not even the finest dilators will pass through the papilla thus rendering necessary a duodenotomy and a papillosphincterotomy under visual control.[9] These manipulations are always followed by submucous hemorrhages and edema of the sphincter and Vater's papilla which may give rise to a fibrosis with some degree of stenosis.[6] To prevent this it is advisable to collocate a rubber catheter of adequate diameter which, extending from the common duct to the duodenum, will pass through the papilla and serve as a support over which the lesions produced by the surgical

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manipulations may heal. To this purpose Catell[5] designed a T tube with long horizontal arms, one of which leads from the common duct to the duodenum by way of Oddi's sphincter and the other of which is cut to the proper size to remain in the proximal duct. Since then this T tube has been widely used in spite of its inherent disadvantages which may be summarized as follows: (1) the possibility of a reflux into the bile duct of the duodenal contents causing a cholangitis if the longitudinal arm is closed; (2) the loss of great quantities of bile and duodenal and pancreatic fluids rich in electrolytes if this arm remains open; (3) the impossibility of taking a postoperative cholangiogram to check the state of the biliary tract before withdrawing the tube.

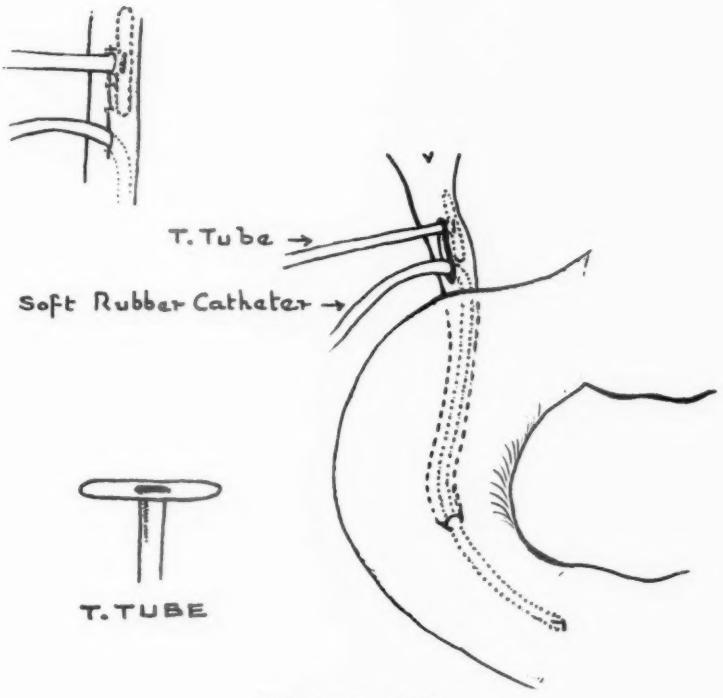

Fig. 1.—See text.

To obviate these disadvantages we use a simple method which consists in placing an ordinary T tube in the common duct with the distal arm sectioned and split so as to leave only half of the circumference (Fig. 1) and through the same opening in the common duct wall a catheter of adequate size, usually 12 or 14 Fr., passing through Oddi's sphincter and Vater's ampulla which has been already dilated or sectioned.

By this method we obtain the following advantages over the method previously employed: (1) the possibility of a reflux of the duodenal contents into the bile ducts or their external loss is eliminated by the simple clamping of this catheter; (2) the free external flow of bile through the T tube is maintained; (3) the collected bile can be injected, if desired, into the duodenum; (4) the duodenal tube can be used for decompressing purposes if necessary; (5) the duodenal tube can be used when required for injecting alimentary

substances (Dripo-lac, etc.); (6) it permits postoperative checking cholangiography before and after the withdrawal of the duodenal catheter; (7) it does not involve any extra operative risk to the patient nor produce of itself any postoperative complications.

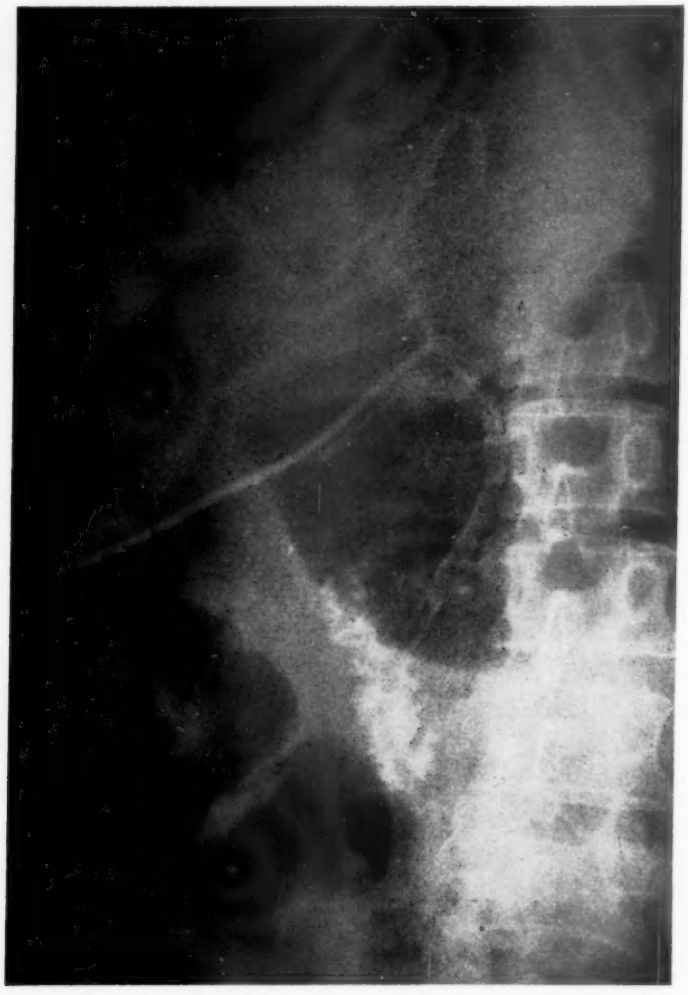

Fig. 2.—Lipiodol has been injected through the T tube while the rubber catheter is kept in place. Notice that the dye has flown freely into the duodenum.

The duodenal catheter must be maintained open during the first few days after operation if a duodenotomy has been performed in order to eliminate the possibility of the distension of the duodenal suture, but should be closed afterwards so that the dilated or sectioned papilla may heal over it. This catheter should be left in position for approximately six weeks, the time necessary for the total healing of the lesions produced during the operation. The T tube can be closed temporarily or permanently to permit the bile to flow to the duodenum since the catheter is no obstacle as we have been able to demonstrate radiologically (Fig. 2). The T tube can remain in the common duct as long as necessary.

Since 1950 we have used this method in 124 cases with good results and without complications.

SUMMARY

A new method with combined drainage tubes in cases of section or dilatation of the sphincter and papilla is presented. Its advantages over the conventional long T tube are emphasized. The procedure has been used by us in 124 cases without complications and with good results.

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EXPERIMENTAL COARCTATION OF THE ASCENDING AORTA

ROBERT A. GAERTNER, M.D., AND ALFRED BLALOCK, M.D., BALTIMORE, MD.

(From the Department of Surgery of the Johns Hopkins University and Hospital)

COARCTATION of the descending thoracic aorta has been produced in the experimental animal and studied by many investigators.[1, 2, 4, 5] Gerbode and Selzer,[3] using a fascia lata ligature to constrict the vessel, produced coarctation in the proximal thoracic aorta, but all the animals were sacrificed in three weeks or less. It is the purpose of this paper to report the technique and results of long-term experiments in which the coarctation was created in the ascending aorta so that the entire arterial vascular bed, excepting the coronary vessels, was distal to the site of constriction. We desired answers to several questions, including the following ones. Would the high pressure in the coronary vascular bed result in an increase in the number of intercoronary communications? Would the high pressure cause coronary arteriosclerosis? Would severe constriction result in hypotension distal to the coarctation, and, if so, what would be the effect on the cerebral and renal circulations?

METHOD

Adult mongrel dogs weighing from 11 to 18 Kg. were used. After premedication with morphine and atropine, the dogs were anesthetized with open-drop ether, an endotracheal tube was inserted, and anesthesia was maintained with a mechanical respirator and ether. The aorta was approached through an incision in the left fourth intercostal space. After dissecting the aorta free, a nonerushing J-shaped clamp was placed so that the lumen of the aorta was almost occluded. The portion of aorta thus excluded by the clamp was excised and the free cut edges were sutured with silk. The clamp was slowly released and bleeding, which usually was slight, was controlled by digital pressure or additional sutures. The chest was closed in layers with silk. Postoperatively pressures were measured by direct needle puncture in the femoral artery and left ventricular cavity. These measurements were made with the animals awake but sedated with morphine.

The coronary circulation was studied by the technique described by Beck.[6] The right coronary artery and circumflex branch of the left coronary artery were cannulated and a mixture of gelatin and barium sulfate was injected into the vessels at a temperature of 45° C. and a pressure of 200 mm. Hg. The degree of filling of the anterior descending branch of the left coronary artery was taken as a measure of intercoronary communications.

Cardiac outputs were measured in some of the dogs by the dye dilution technique and/or the direct Fick principle utilizing right heart catheterization.

RESULTS

Coarctation of the ascending aorta was produced in a total of 18 dogs. Of these, 6 died of various causes (rupture of the suture line, cardiac tamponade

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following ventricular puncture, or empyema) before they had been adequately studied. Twelve dogs were followed for four to thirty months before they were sacrificed.

The degree of coarctation varied from animal to animal. In 8 of the dogs, roentgenograms were taken of the aortic arch while it was filled with a Diodrast solution under a pressure of 200 mm. Hg. Two of these roentgenograms are illustrated in Fig. 1. Measurements were made from the films so that the relative degree of constriction could be calculated. These results are presented in Table I. It can be seen that the cross-sectional area of the aortic lumen was reduced to as little as 11 per cent of the area of the aorta proximal to the constriction and that in only 2 cases was there an increase in the size of the poststenotic region. These increases were only slight and could not be called poststenotic dilatation.

TABLE I. DEGREE OF COARCTATION

	CROSS-SECTIONAL AREA		
EXP. NO.	PROXIMAL AORTA SQ. CM. (PER CENT)	COARCTATION SQ. CM. (PER CENT)	DISTAL AORTA SQ. CM. (PER CENT)
1	3.14 (100)	0.38 (12)	2.83 (90)
5	1.77 (100)	0.28 (16)	1.54 (87)
6	3.14 (100)	0.50 (16)	2.54 (81)
7	2.98 (100)	0.64 (22)	2.40 (81)
8	2.54 (100)	0.28 (11)	1.33 (52)
10	2.54 (100)	0.79 (31)	2.69 (106)
11	2.83 (100)	1.77 (63)	2.54 (90)
12	3.97 (100)	1.13 (29)	4.52 (114)

Left ventricular and femoral artery pressures were measured at varying intervals following operation. Table II contains the final pressures obtained. In general, if a significant degree of coarctation was produced, the pressure in the left ventricle rose gradually over the first two months and then remained more or less constant. There was a parallel rise in femoral artery pressure. No animal developed hypotension distal to the area of constriction.

TABLE II. LEFT VENTRICULAR AND FEMORAL ARTERY BLOOD PRESSURES (MM. HG)

EXP. NO.	LEFT VENTRICLE	FEMORAL ARTERY	MEAN FEMORAL	TIME POSTOPERATIVE (MONTHS)
1	280	175/115	135	9
2	290	175/120	135	9
3	250	190/120	155	14
4	250	130/90	105	14
5	250	160/100	110	30
6	225	175/110	130	14
7	220	170/100	125	5
8	200	150/90	125	22
9	200	150/105	120	8
10	170	160/100	130	2
11	160	160/90	115	4
12	165	125/90	110	4

Cardiac outputs were measured postoperatively in 6 of the dogs and these results are listed in Table III. Although preoperative cardiac outputs were not measured, at least it can be said that the experimental coarctation did

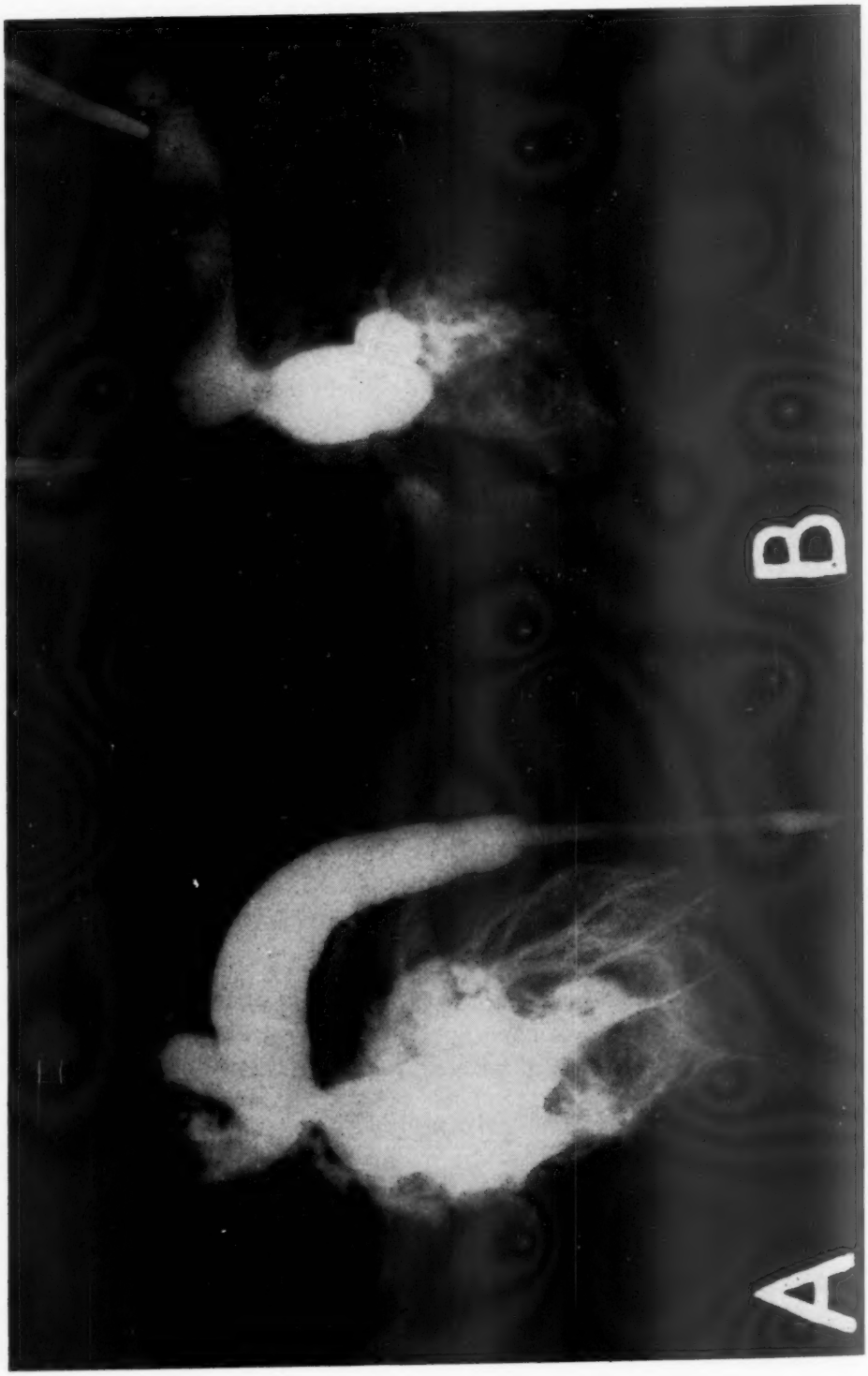

Fig. 1.—Post-mortem aortograms of the coarctations of 2 dogs. *A*, Dog No. 1. Nine months postoperative. Left ventricular pressure 280 mm. Hg. Cross-sectional area of coarctation 0.38 sq. cm. or 12 per cent of that of proximal aorta. *B*, Dog No. 6. Fourteen months postoperative. Left ventricular pressure 225 mm. Hg. Cross-sectional area of coarctation 0.50 sq. cm. or 16 per cent of that of proximal aorta.

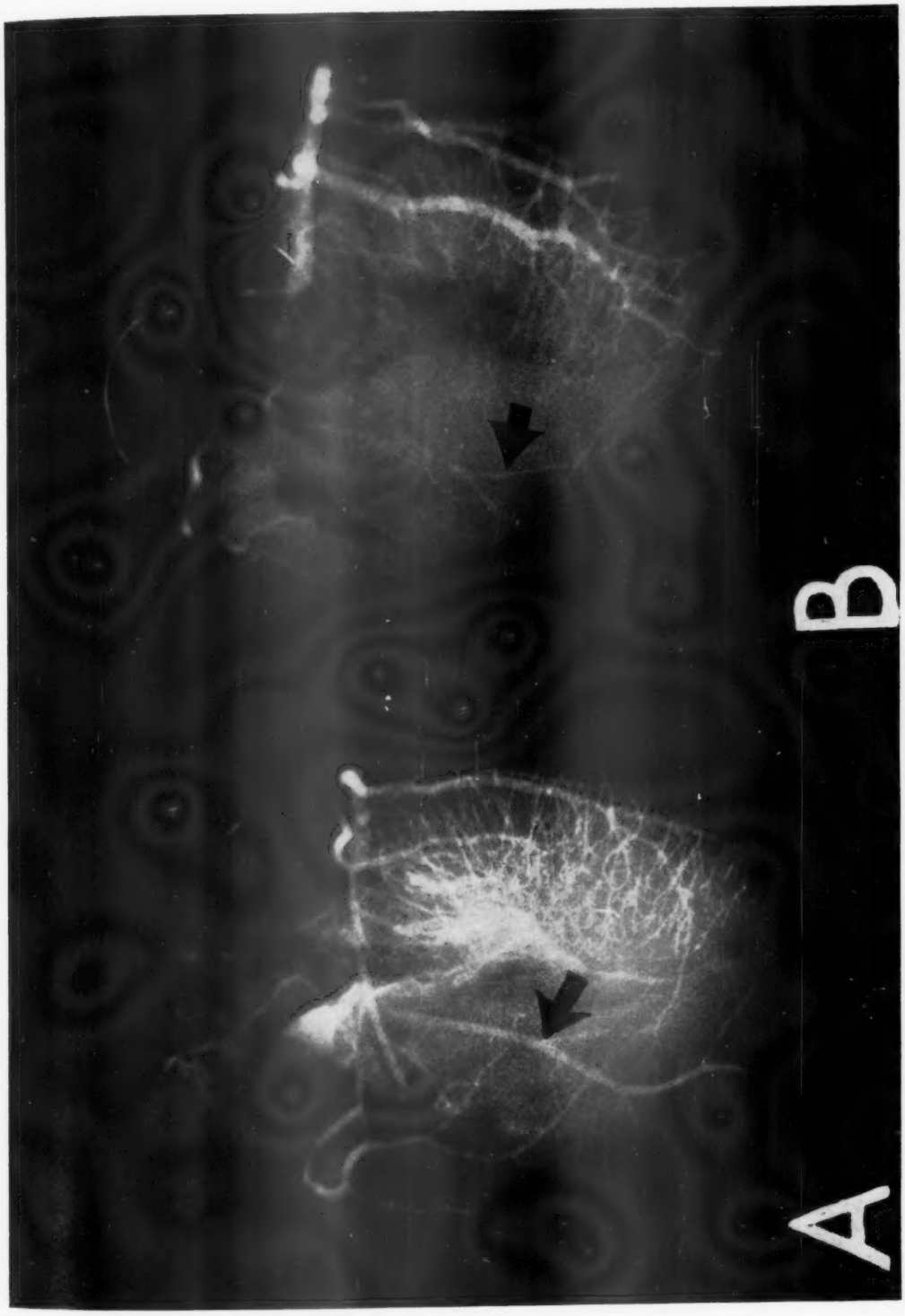

Fig. 2.—Roentgenograms of the coronary arteries after injection with a barium sulfate-gelatin mixture at 200 mm. Hg. *A*, Dog No. 3. One of the 2 dogs showing good filling of the anterior descending branch of the left coronary artery. *B*, Dog No. 9. One of the dogs showing minimal filling of the anterior descending branch of the left coronary artery. This same amount of filling is seen in control animals.

not result in low cardiac outputs. Thus, despite the increased resistance to flow produced by the coarctation, the left ventricle was capable of compensating and maintaining an adequate output.

In 12 animals, the coronary arteries were injected at the time of death or sacrifice. A control group of 10 normal dog hearts were injected using the same technique. The degree of filling of the anterior descending branch of the left coronary artery was taken as an index of intercoronary anastomoses. In the control group there was either no filling of the anterior descending branch or slight filling of the distal third of that artery. In the coarctation group, 10 of the 12 dogs studied showed no significant difference from the control group (Fig. 2, *B*). However, two dogs showed good filling of the artery indicating that a number of intercoronary communications had been present prior to or had developed following the operation (Fig. 2, *A*). None of the dogs showed any signs of left- or right-sided heart failure.

TABLE III. POSTOPERATIVE CARDIAC OUTPUTS

EXP. NO.	TECHNIQUE	OUTPUT (L./MIN.)	OUTPUT/KG. (C.C./KG./MIN.)
6	Fick	4.10	248
2	Dye dilution	3.63	214
	Fick	3.56	198
11	Dye dilution	2.87	197
7	Fick	2.64	230
	Dye dilution	2.24	185
10	Dye dilution	1.88	163
8	Dye dilution	1.78	127

At the time of death or sacrifice a complete autopsy was performed. Moderate hypertrophy of the left ventricle was found in all the long-term survivors. Otherwise gross examination of all the dogs showed no abnormalities except for those animals that died with empyema, rupture of the suture line, or cardiac tamponade. Examination of multiple sections taken from the brain, kidney, liver, spleen, lung, myocardium, aorta, and coronary arteries failed to show any consistent significant deviation from normal.

DISCUSSION

In the majority of experiments reported in this paper, the area of the lumen of the aorta was reduced to less than 30 per cent of that of the aorta proximal to the coarctation. In 2 animals it was 11 and 12 per cent. Under these circumstances one would expect a decrease in flow through the aortic arch. However, when cardiac outputs were measured, they were not low. Furthermore, the pressure in the femoral artery was not low in any of the dogs. Undoubtedly the increase in ventricular pressure which developed in the postoperative period resulted in a large blood flow in spite of the increased resistance.

There was no evidence in most of the dogs of an increase in intercoronary communications. Since the ostia of the coronary arteries are proximal to the area of coarctation, the coronary vessels are subjected to a high mean aortic pressure and undoubtedly the coronary flow is increased. It would seem that coronary flow keeps pace with ventricular hypertrophy and there is no stimulus for the formation of intercoronary anastomoses. This conclusion is supported by the fact that none of the dogs developed signs of left-sided heart failure.

SUMMARY

1. Twelve dogs with coarctation of the ascending aorta were observed for periods varying from four to thirty months.

2. The smallest cross-sectional area of constriction was only 11 per cent of that of the proximal aorta.

3. In only 2 dogs was there radiologic evidence of an increase in intercoronary anastomoses.

4. There was no evidence of coronary arteriosclerosis.

5. Despite the marked aortic constriction, the cardiac output was normal or high.

6. The blood pressure in the systemic arteries distal to the site of coarctation was normal or elevated.

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A TECHNIQUE OF ABDOMINAL AORTOGRAPHY AND FEMORAL ARTERIOGRAPHY

CHARLES V. MENENDEZ, M.D., AND ROBERT R. LINTON, M.D., BOSTON, MASS.

(From the Peripheral Vascular Laboratory and the Radiological Department of the Massachusetts General Hospital)

TRANSLUMBAR AORTOGRAPHY

AORTOGRAPHY was first described in 1929 by Dos Santos[3] of Portugal, but the method was not popularized until 1941 by Farinas[4] of Cuba. Nelson[8] of Seattle, in 1942, reported the first cases performed in the United States. An enormous number of aortograms have been done to date, considering that Melick and Vitt,[6] in 1948, collected 3,000 cases from the literature.

The purpose of this paper is to describe a simple method of abdominal aortography and femoral arteriography which can be performed in the smallest hospitals, using standard equipment, and by means of which satisfactory arteriograms may be obtained.

Anesthesia.—Aortography may be carried out under local anesthesia alone or combined with intravenous sodium thiopental anesthesia. If the patients are psychologically unsuited for local anesthesia, or if any technical difficulty is anticipated, as with severe arthritis of the vertebral spine, thiopental is preferred. Poor cardiac risks are given local anesthesia. With thiopental, it is essential that considerable depth of anesthesia be obtained to prevent motion of the patient as the dye is being injected; otherwise, blurring of the film will occur. It is helpful, also, with thiopental, to halt deep respiration preliminary to dye injection either by sudden administration of the total anesthetic dose, and/or by a short period of forced assisted breathing through an oxygen mask. The usual method is to perform, under local anesthesia, the initial portion of the procedure to the point at which the aorta has been entered and the dye-containing syringe has been attached. The sodium thiopental is then administered. By this means, a minimal amount of the intravenous anesthetic is used.

When local anesthesia is employed, the patient is forewarned of what to expect. He is informed that he will feel a great heat descend through the abdomen, particularly into the perineum, and pass down the lower extremities to the feet, depending upon the patency of the arteries which supply each lower extremity. He is encouraged to brace himself, to refrain from moving, and to hold his breath. Reassurance is given that the intense sensation will last momentarily and that the nausea, rarely retching, which follows will subside in a few minutes.

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Preparation.—For aortography preoperative preparation includes: withholding oral intake for several hours, a saline enema to reduce distorting gas shadows to a minimum, and Demerol (with atropine if sodium thiopental is to be employed) administered subcutaneously just prior to the procedure.

Patient's Position and X-ray Technique.—The patient reclines face downward on the x-ray table over which is placed, at the head end, a lead apron. The 14- by 17-inch casette within the Potter-Bucky diaphragm is positioned lengthwise beneath the patient so that the film extends cephalad to include the twelfth thoracic vertebra. A 14- by 17-inch grid casette containing a slow speed film (DuPont No. 502), with an ordinary sheet of film-package paper placed over the posterior screen of the casette, is centered lengthwise on the top of the table beneath the patient's thighs. The tablet-top casette is adjusted so that its upper

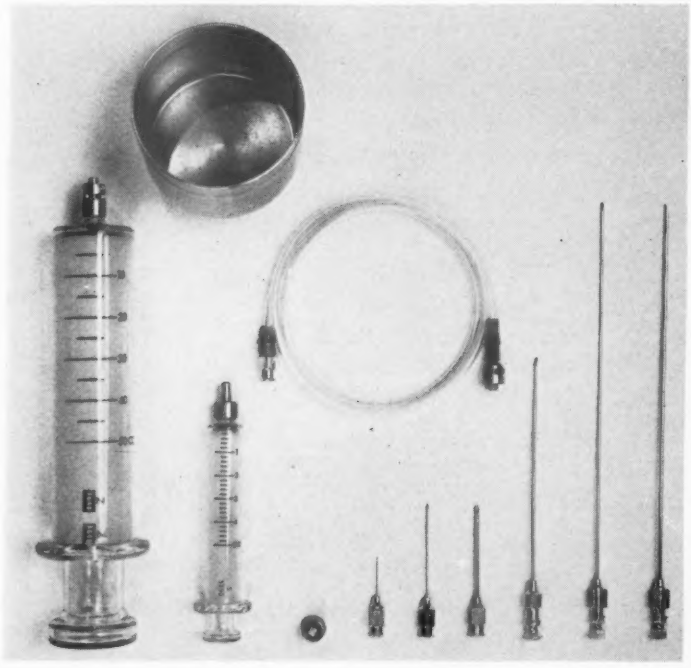

Fig. 1.—Instrument set for lumbar aortography and femoral arteriography. The articles from left to right are as follows: (1) 50 c.c. syringe for iodopyracet (Diodrast), (2) 5 c.c. syringe for procaine, (3) metal cup for iodopyracet (Diodrast), (4) metal plug, (5) polythene tubing, (6) No. 25 needle for procaine wheal, (7) No. 22 needle for subcutaneous infiltration of procaine, (8) No. 15 needle for removing procaine from ampule, (9) No. 18 needle and stylet for femoral arteriography, (10) No. 18 needle and stylet, 6 inches in length, for procaine infiltration in aortography, (11) No. 16 needle and stylet, 6 inches in length, for translumbar aortography.

edge accurately approximates the lower edge of the Potter-Bucky film. Another lead apron is then carefully laid over the patient's lower buttocks and thighs to completely shield the lower film, but not to encroach upon the upper one. A sandbag may be used to support the ankles for comfort and to protect the toes by elevating them from the table top if any ischemic lesions exist. A compression band over the lower legs aids in preventing involuntary movement. If no occlusion is present in one extremity, and all pulsations (femoral, popliteal, dorsalis pedis, and posterior tibial) are full and bounding, a sphygmomanometer cuff, applied to the upper thigh, may be inflated just prior to aortography to force a

greater concentration of contrast material into the involved limb. The x-ray tube is raised approximately 54 inches from the surface of the table and is centered directly over the two overlapping edges of the x-ray films. One hundred Ma. are employed. The average kilovoltage used is 68 to 70, with extremes of from 65 to 80, depending upon the size of the patient. A preliminary abdominal film is obtained to inspect its quality from the standpoint of x-ray technique, and also

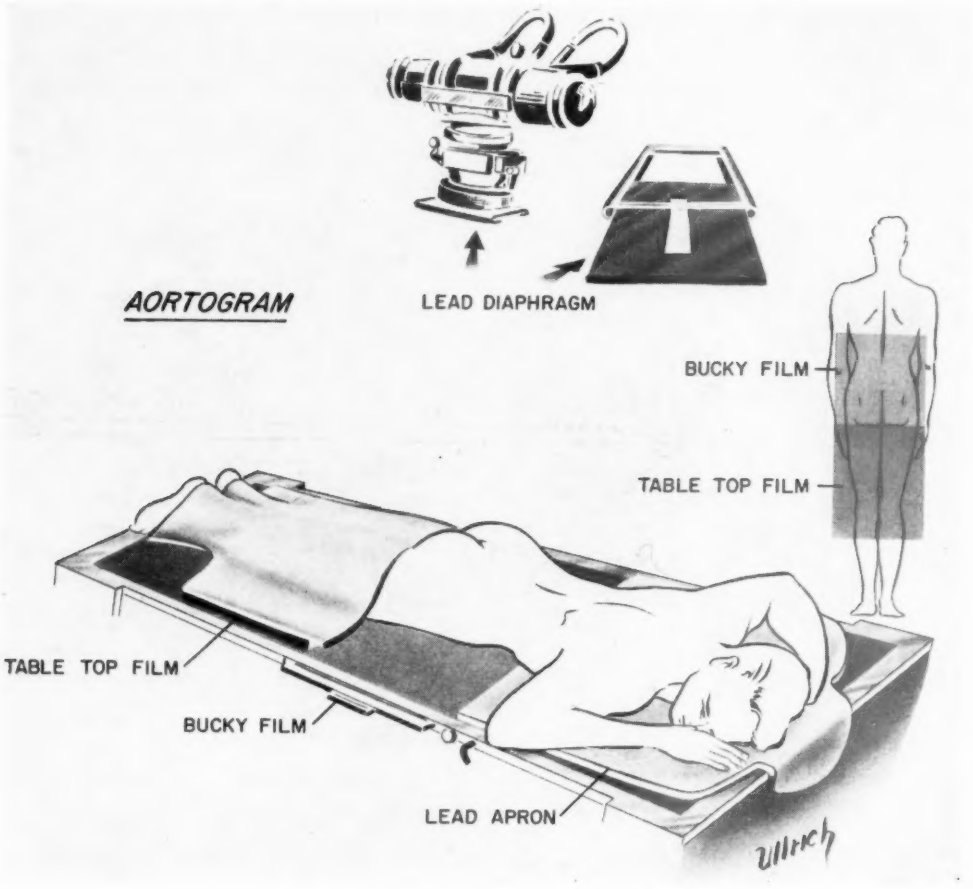

Fig. 2.—Position for aortography.

to note its position in relation to the patient. As mentioned above, the inclusion of the twelfth thoracic vertebra on the film indicates a satisfactory level. The renal arteries are located approximately at L_2, and in both obliterative aortic disease and in aortic aneurysm, knowledge of the status of the renal arteries and of the aorta just proximal to them is important. Other values of the check film include discovering buttons or pins on clothes, residual barium from other x-ray examinations, or the absence of a twelfth rib. In the case of a rudimentary twelfth rib, or one difficult to palpate in an obese patient, advancement of the needle through the eleventh interspace may traverse the pleural space. Although this has been done inadvertently without incident, it is probably wise to be aware of it.

Needle Insertion.—The aortographer prepares and drapes the skin. Sterile gloves are worn. An intradermal procaine wheal is made just beneath the lower edge of the twelfth rib, about 7 cm., or slightly more in stout individuals, to the left of the midline. By means of a 6-inch, No. 18 needle, advanced medially and slightly superiorly, procaine is injected along the proposed tract to the aorta. Frequently the body of the first lumbar vertebra is encountered. By a process of continual withdrawal and insertion, it can be "walked" anteriorly over the edge of this bony prominence to reach the aorta.[2, 5, 10] At other times the bone is not identified and instead the pulsating thrust of the aortic wall is felt slightly farther along. The No. 18 needle is withdrawn when the aorta is reached and in its place is inserted a No. 16 needle of the same length. It has been found that the smaller bore needle can be more easily and more accurately manipulated with less trauma; in other words, locating the aorta and anesthetizing the tract are more easily accomplished with the smaller gauged needle. Entrance of the needle into the aorta at the level of L_1 enables one to obtain an aortogram in the presence of aortic thrombosis up to the renal arteries. After entering the aorta with the No. 16 needle, it is advanced for a few millimeters to prevent extravasation of the dye on injection. The stylet is then placed within the needle; all prior maneuvering with the No. 16 needle through procainized tissue having been done without the stylet in place in order to be aware, by the appearance of a pulsating jet of blood, of the immediate moment the aortic wall has been punctured. Usually between 1 and 2 inches of the needle remain visible after the aortic lumen has been entered. A gauze sponge held adjacent to the needle end, with the stylet near at hand, will avoid unnecessary soiling of the patient's skin and the table top with blood. The segment of polythene tubing, previously filled with dye, and free of air bubbles, is connected to the needle. A small metal plug is employed to seal the open end of this plastic tube. Twisting of the needle, which may dislodge its tip, can be avoided by attaching the 50 c.c. syringe to the polythene tubing, after, rather than before, the tubing has been joined to the needle. This tubing may be pinched shut while the syringe is being fastened on.

Protection.—Shielding the aortographer from the roentgen rays is an important consideration and, for this purpose, many methods may be devised. A standard lead apron is useful for the occasional aortographer and a small lead shield for the hands is also worth while. To protect individuals frequently exposed, a more elaborate device is essential. A lead shield, which may be rolled between the operator and the patient, is extremely effective. The tubing may be passed around it. A cone or diaphragm* should be attached always to the roentgen tube to prevent unnecessary scattering of rays.

Contrast Material.—Fifty to sixty cubic centimeters of 70 per cent iodopyracet (Diodrast) is injected as rapidly as possible, requiring usually about 6 to 7 seconds. It has been customary to add 15 to 20 c.c. of 35 per cent iodopyracet

*Satisfactory measurements, using the technique described in this presentation consist of rectangular opening 7.5 cm. by 3 cm. in an area centrally located in a lead sheet of 4 mm. thickness.

(Diodrast) to the 50 c.c. of 70 per cent iodopyracet in order to fill the plastic tubing and allow for sensitivity testing. Iodopyracet, though said to be more viscous, is preferred to other contrast substances because it has been found to be less painful. This observation has been made in both aortography and arteriography under local anesthesia.

Exposure.—In aortography techniques employing a rapid exposure, the bolus of dye is "stopped" and only a portion of the vascular tree is visualized. *Two prolonged exposures of 2.5 seconds each is the chief feature of this method of aortography.* By this means, the dye may be followed from the upper abdominal aorta down to the popliteal bifurcation. This method of contrast radiography may be compared to an ordinary camera photograph of a moving light source at night, using a time exposure. A continuous tracing of the motion of the light is obtained. The first exposure is begun when approximately 25 c.c. of solution remains in the syringe. As soon as the injection is completed the syringe is set aside placing the operator, immediately after completion of the first exposure, in readiness to remove the apron covering the lower extremities and to slide the Potter-Bucky diaphragm cephalad until it is beneath the apron shield on the table top before calling for the second exposure. This maneuver, which usually requires about 2 or 3 seconds, should be made as rapidly as possible.

Timing.—The above technique applies to the more commonly encountered cases of partial aortic or unilateral iliac thrombosis. With a palpable femoral pulse on either side, in the absence of an abdominal aortic aneurysm, speed is essential, and the second exposure should be obtained as soon as possible after the first one. Injection of the syringeful of 70 per cent iodopyracet (Diodrast) should require, as previously stated, about 6 or 7 seconds, and a time lapse of about 7 seconds should take place between the starts of the first and second exposures. In patients with bilateral absence of palpable femoral pulses from advanced aortic bifurcation or iliac obliteration, a longer time interval is desirable. It is recommended that the maneuver be carried out in this second group with an interval of about 10 or 12 seconds between the beginnings of the two exposures. Obtaining satisfactory films of abdominal aortic aneurysms, especially larger ones, necessitates a slight modification of the injection technique. A pause is essential after the injection is made, but before the exposure is begun, in order to permit the dye to reach the iliac vessels. This mixing period of the contrast substance and blood within the aneurysmal sac varies, of course, considerably, depending upon the amount of clot contained within the sac, and may be markedly shortened when the entire aneurysm, except for a narrow lumen, is filled with clot. An effective method, however, consists of injecting about two-thirds of the syringeful of 70 per cent iodopyracet (Diodrast) followed by a delay of a number of seconds as indicated in the accompanying tables, before starting the exposure. Then, *while the exposure is in progress,* the final one-third syringeful is rapidly introduced. This produces a clear outline of the upper extent of the aneurysm so that its relation to the renal arteries can be accurately determined.

Indications.—In patients being considered for aortic resection and grafting for abdominal aortic aneurysm, it is worth while to know if the renal arteries are involved. Whether or not the dilatation includes the iliac vessels may be valuable information, also, because in patients without actual iliac involvement, a "sleeve" graft rather than a bifurcation may be inserted. When thrombosis

Fig. 3.—Normal aortogram except for slight elongation of aorta and normal femoral arteriograms.

of the aorta or iliac vessels exists, this method of prolonged exposure allows time for the distal patent vessels to be filled with the dye; and obtaining simultaneous femoral arteriograms reveals the status of the femoral arteries without the necessity of separate arteriographic procedures for their visualization. When a patent popliteal artery is present in spite of extensive thrombosis of the aortic bifurcation, iliac, and femoral vessels, insertion of a long by-pass graft is sometimes possible, and may be a limb-saving procedure.

Fig. 4. Fig. 5.

Fig. 4.—Normal aortogram with arteriograms showing thrombosis in left femoral artery. Peripheral pulsations were strong throughout right lower extremity.

Fig. 5.—Aortogram showing some stenosis of bifurcation, with arteriograms depicting thrombosis in left femoral artery.

Precautions.—On a few occasions, the thiopental anesthetized patient has arched his back markedly a few moments after the injection. The needle has been immediately withdrawn to prevent injury to the aorta. Otherwise, the stylet is replaced and the films are developed. Another injection may be given if for one reason or another the initial films are unsatisfactory. Faulty equipment or developing technique occasionally are causes of unsatisfactory films. If the films are adequate, an abdominal film for a pyelogram is obtained and

Fig. 6. Fig. 7.

Fig. 6.—Aortogram showing thrombosis of left common iliac artery, with normal femoral arteriograms.

Fig. 7.—Aortogram showing thrombosis of right common iliac artery, with arteriograms depicting thrombosis in left femoral artery.

the needle is withdrawn. Should extravasation have occurred, injection of 10 to 20 c.c. of dilute procaine or a longer acting local anesthetic and 500 c.c. of normal saline solution is recommended (before removal of the No. 16 needle) into the para-aortic tissue. Because of the danger of renal insult by aortography, urinary output should be recorded for a few days following the procedure.

Fig. 8.—Aortogram showing large aortic aneurysm extending up to renal arteries, with normal femoral arteriograms. Note calcification on abdominal film.

When no pulsations are palpable, it is assumed that complete aortic thrombosis distal to the renal arteries may be present. In such patients, 50 c.c. of 35 per cent iodopyracet (Diodrast) is employed, rather than the 70 per cent concentration, to avoid renal injury.[1]

If aortic or iliac thrombosis is incomplete, so that the majority of the contrast material does not enter the renal arteries, and if better delineation is desired, the aortogram may be repeated using concentrated dye. Checking each article in the set of equipment for leaking or ill-fitting connections, incorrect, broken, or absent parts, and so forth, is recommended before undertaking the procedure. Care should be taken to prevent blood, glove powder, or contrast dye from coming into contact with the syringe plunger, or "sticking" will take place. If this occurs the syringe plunger should be rinsed off with any sterile solution, as procaine, saline, etc., before being used. The usual sensitivity tests have not been carried out. However, just prior to the main injection of iodopyracet (Diodrast) a few cubic centimeters of the contrast material are introduced, followed by a pause of 2 or 3 minutes. A serious sensitivity would become apparent if it existed.

Complications.—Delayed, mild, transient, urticarial reactions have occurred in a few patients, but there have been no serious complications.[1, 7] Complete extravasation of 50 c.c. of 70 per cent iodopyracet (Diodrast) has occurred in 2 patients. Severe substernal pain was produced, which persisted for several

*Table I (A). Aortography: Thrombosis

	Time recommended for injection of 50 to 60 c.c. of 70 per cent Diodrast (approximate)	Amount of 70 per cent Diodrast remaining in syringe when exposure first begun (approximate)	Time interval between start of first exposure (abdominal film) and start of second exposure (film under thighs) (approximate)
Partial aortic or unilateral iliac thrombosis	6 to 7 seconds	20 to 25 c.c.	7 to 8 seconds

Table I (B). Sequence in Aortography: Partial Aortic or Unilateral Iliac Thrombosis

I	II	III	IV
Rapid injection of approximately 35 to 40 c.c. of 70 per cent Diodrast	First exposure (abdominal film) started Completion of I with rapid injection of remaining 20 to 25 c.c. of 70 per cent Diodrast while first exposure in progress	Shielding of abdominal and uncovering of film under thighs (requiring 2 to 3 seconds)	Second exposure (film under thighs) started

*The tables have been prepared to assist in having the x-ray films taken at the proper time. As previously stated, deciding when to signal for the exposure in order to catch the dye within the desired arteries is the most difficult phase of this diagnostic procedure. Occasionally only by trial and error will a satisfactory roentgenogram be obtained. The rate of blood flow depends primarily upon patent arterial channels, the size and number of which can only be estimated. Volumes and times, therefore, in an individual case, may be found to vary from those indicated. Each pair of the following tables describes the same technique in a different manner in an attempt to facilitate understanding of the method.

hours and opiates were required for relief. There were no other sequelae. In several patients, extravasation of a few cubic centimeters of dye has taken place with no remarkable effects other than transitory discomfort.

TABLE II (A). AORTOGRAPHY: ANEURYSM

SIZE OF ABDOMINAL AORTIC OR ILIAC ANEURYSM* (APPROXIMATE)	DELAY BETWEEN FIRST PORTION (30 TO 35 C.C. OF 70 PER CENT DIODRAST) AND SECOND PORTION (20-25 C.C. OF 70 PER CENT DIODRAST) OF INJECTION (APPROXIMATE)	TIME INTERVAL BETWEEN START OF FIRST EXPOSURE (ABDOMINAL FILM) AND START OF SECOND EXPOSURE (FILM UNDER THIGHS) (APPROXIMATE)
Small: 6 to 8 cm. in diameter	2 to 3 seconds	7 to 8 seconds
Medium: 10 to 12 cm. in diameter	4 to 5 seconds	9 to 10 seconds
Large: 15 or more cm. in diameter	6 to 7 seconds	11 to 12 seconds

*Estimations by physical examination and by calcification in abdominal roentgenogram.

TABLE II (B). SEQUENCE IN AORTOGRAPHY: ANEURYSM

	I	II	III	IV	V	VI
Small aneurysm	Rapid injection of approximately 30 to 35 c.c. of 70 per cent Diodrast	Pause for approximately 2 to 3 seconds	First exposure (abdominal film) started Completion of I with rapid injection of remaining 20-25 c.c. of 70 per cent Diodrast while first exposure in progress	Shielding of abdominal film and uncovering of film under thighs (requiring 2 to 3 seconds)	Pause for approximately 2 to 3 seconds	Second exposure (film under thighs) started
Medium aneurysm	As above	Pause for approximately 4 to 5 seconds	As above	As above	Pause for approximately 4 to 5 seconds	As above
Large aneurysm	As above	Pause for approximately 6 to 7 seconds	As above	As above	Pause for approximately 6 to 7 seconds	As above

FEMORAL ARTERIOGRAPHY

Anesthesia.—Femoral arteriograms have been performed by the percutaneous route under local infiltration anesthesia.*

Preparation.—Food is withheld for a few hours prior to arteriography because of the nausea and occasional vomiting produced by iodopyracet (Diodrast). Premedication consists of a hypodermic injection of Demerol. Shaving of the groin is not necessary.

Patient's Position.—The patient is placed supine on the x-ray table with the extremity to be examined in the center of the table. A 14- by 17-inch casette within a Potter-Bucky diaphragm is adjusted lengthwise to include the thigh

*Intravenous sodium thiopental has been rarely necessary.

and the groin. On the table top beneath the patient's lower leg is placed lengthwise a 14- by 17-inch grid casette containing a slow speed film (DuPont No. 502) with a paper covering the screen on the posterior surface of the casette. A few millimeters of overlap of these 2 films will insure that a hiatus does not exist between them. A compression band, snuggly drawn over the patient's knee, will aid in preventing inadvertent motion of the limb. Small sandbags may be used to support the foot and maintain it in a position perpendicular to the surface of the table.

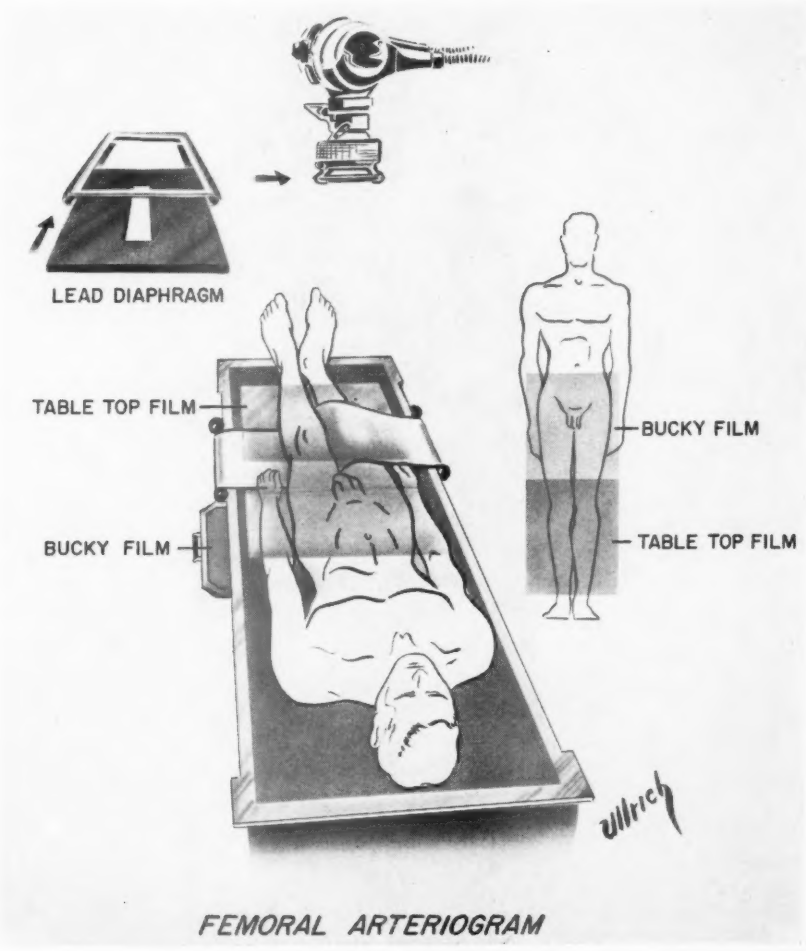

Fig. 9.—Position for femoral arteriography

X-ray Technique.—As with aortography, the x-ray tube is raised approximately 54 inches from the surface of the table and is centered immediately above the 2 overlapping edges of the x-ray films. The majority of arteriograms in this series have been performed with an *exposure time of 2.5 seconds.* Milliamperage has been 100, and average kilovoltage has been 60 with a range of from approximately 55 to 65.

Recently, however, it has been found that accurate arteriograms can be obtained in extremities with marked arterial occlusion by using an *exposure time of 5 seconds.* As stated, this greatly prolonged exposure time is reserved as an alternate method for cases in which there is extreme diminution in the rate of blood flow. Longer exposure times than 5 seconds have been found to be unsatisfactory. In using the 5-second exposure, milliamperage has been 50 and average kilovoltage has been 65 with a range of from approximately 60 to 70.

A preliminary film to test the technique, positioning, etc., is usually worth while, but may be dispensed with if sufficient practice proves it unnecessary.

Insertion of the Needle.—The groin is prepared with an antiseptic solution. A sterile towel is draped over the thigh and sterile gloves are worn. A procaine wheal is made in the groin over the pulsation of the femoral artery, and the subcutaneous tissue overlying this vessel is infiltrated. A 4-inch No. 18 spinal needle, the stylet of which has been removed, is then inserted in a cephalad direction into the common femoral artery. It has been found that directing the needle caudad makes entrance into the artery more difficult because the vessel is less firmly attached to the surrounding tissue and rolls from under the point of the needle. When the artery has been entered and a forceful stream of arterial blood appears, the stylet is inserted. A polythene tube previously filled with dye is attached to the arterial needle, after removal of the stylet, in the same manner as in aortography. In performing a femoral arteriogram, it is most important to prevent motion of the needle to avoid its dislodgment from the arterial lumen. Pinching of the plastic tubing between the thumb and forefinger, removal of the metal plug, and attachment of the dye-filled 50 c.c. syringe may be easily carried out. The patient is informed that the discomfort to be experienced will consist of an intense burning which will pass distally from the groin, down the lower extremity, and into the foot. He is reasurred that it will be momentary, and is requested to brace himself in preparation for it. Following the injection, the stylet is replaced and the films are developed. A pyelogram may be obtained in about 5 minutes after dye introduction if desired. Should the films be unsatisfactory, or should better delineation of a particular portion of the vascular tree be needed, another arteriogram may be obtained without danger.

Protection.—The same precautions should be taken for shielding the operator as in aortography.

Contrast Material.—Approximately 50 to 60 c.c. of 35 per cent iodopyracet (Diodrast) has been employed for femoral arteriography. Three 30 c.c. ampules of 35 per cent iodopyracet (Diodrast) are opened to provide an amount sufficient to fill the plastic tubing and to perform the circulation time test. No intra-arterial procaine has been used.

Circulation Time.—The correct timing of the x-ray exposure is one of the difficult phases of femoral arteriography as the speed of the circulation varies with the degree of arterial obliteration. Testing of the circulation time is carried out routinely before the arteriogram is obtained. The extreme usefulness of this preliminary maneuver should be emphasized. It enables the

arteriographer to estimate the rate of blood flow in the extremity so that the exposure may be made at the optimum time. Ten cubic centimeters of 35 per cent iodopyracet (Diodrast) is rapidly injected and the patient is asked to signify when a sensation of warmth reaches the knee and the ankle. If a short segment of occlusion exists, with good collaterals, warmth will usually be felt around the knee in about 10 seconds and at the ankle in about 20 seconds. Patients, however, with complete obliteration of the superficial femoral artery will usually not feel the warmth reach the knee at all, but will note that it becomes dissipated and ceases in the thigh. Repeating the arteriogram with a change of timing is sometimes necessary to obtain satisfactory films, especially of the all-important popliteal artery.

Timing With 2.5 Second Exposure.—The solution of 35 per cent iodopyracet (Diodrast) is injected as rapidly as possible to obtain the arteriogram in case of minimal involvement, with the signal to begin the exposure being given when approximately 10 or 15 c.c. of dye remain in the syringe. If moderate thrombosis is suspected, the start of the exposure may be delayed until almost all of the solution has been injected, and the rate of injection may be slowed slightly. This will afford the dye time to fill the arteries of the lower leg completely. With extensive thrombosis, a slight modification of technique is employed. Approximately two-thirds of the syringeful of 35 per cent iodopyracet (Diodrast) is injected. A pause is then made for a varying number of seconds, depending on the anticipated extent of thrombosis, and the remaining one-third syringeful of iodopyracet (Diodrast) is then injected with the exposure being started when about 10 to 15 c.c. of solution remain. Estimating this time interval, or pause, can be done by clinical evaluation and by the circulation-time test. If the claudication is long standing and marked, 4 to 5 seconds will be required. In more extensive obliterative disease with, in addition to severe claudication, rest pain and ischemic necrosis of the foot, 7 or 8 seconds may be necessary. When a popliteal aneurysm is present, similar "delayed-action" technique is employed. Approximately one-half the syringeful is injected before the pause is made, with the delay in time varying according to the size of the aneurysm. The exposure is begun when approximately 10 to 15 c.c. of the solution remain in the syringe. It should be cautioned, however, that when palpable pulses are absent at the ankle distal to the aneurysm, the emptying time of the aneurysm will be considerably prolonged, and an interval of delay a few seconds longer as indicated in Tables IV (A) and IV (B) will be required to visualize the outflow tract.

Timing With 5-Second Exposure.—In cases of extreme slowing of the circulation due to marked femoropopliteal thrombosis and poor collateral circulation, this alternate technique may be used. As indicated in Table III (B) the injection is given at a slower rate and the exposure is started when about 15 c.c. of dye remain in the syringe.

Indications.—An accurate arteriogram is an essential prerequisite to grafting procedures, especially in patients with degenerative obliterative arterial

Fig. 10. Fig. 11. Fig. 12.

Fig. 10.—Normal femoral arteriogram.
Fig. 11.—Femoral arteriogram showing thrombosis in superficial femoral artery.
Fig. 12.—Femoral arteriogram showing functioning by-passing graft.

disease. It is considered important to by-pass, by means of a vascular graft, as much of the diseased artery as possible by placing the proximal and distal sites of anastomoses in the most normal segments of the arterial tree.

Precautions.—Sensitivity is tested, as with aortography, by the introduction of a few cubic centimeters of 35 per cent iodopyracet (Diodrast) into the artery immediately prior to testing the circulation time and by observing for a few minutes if any noticeable sensitivity exists. Some of the safeguards mentioned under aortography pertain also to femoral arteriography.

Complications.—There have been no remarkable complications. It is believed that cases of acute arterial insufficiency reportedly precipitated by arteriography are probably due to the trauma of the needle puncture. It is conceivable that a large intimal plaque may be elevated mechanically with serious consequence. This would seem more likely with the use of larger needles through which a polyethylene tube may be threaded. The effect of iodopyracet (Diodrast) has been investigated experimentally by Shaw,[9] and a period of momentary vasoconstriction followed by a somewhat longer interval of dilatation was found to occur after Diodrast injection, as outlined above for femoral arteriography. Varying amounts of extravasation have occurred in several patients,

TABLE III (A). ARTERIOGRAPHY: FEMORAL ARTERY OCCLUSION

	TIME RECOMMENDED FOR INJECTION OF 50 TO 60 C.C. OF 35 PER CENT DIODRAST*	APPROXIMATE AMOUNT OF 35 PER CENT DIODRAST REMAINING IN SYRINGE WHEN EXPOSURE BEGUN
Minimal thrombosis, short block in superficial femoral artery, moderate claudication	Approximately 9 to 10 seconds	15 c.c.
Moderate thrombosis, long block in superficial femoral artery, marked claudication, moderate rest pain	Approximately 11 to 12 seconds	5 to 10 c.c.
Moderate thrombosis, alternate method	Injection given in two parts 1. Approximately 30 to 35 c.c. solution injected in about 6 to 7 seconds Pause for 2 to 3 seconds 2. Inject remaining 20 to 25 c.c. solution at same rate as first portion	10 to 15 c.c.
Marked thrombosis, precarious lower extremity, constant severe pain, ischemic skin lesion	Injection given in two parts 1. Approximately 30 to 35 c.c. solution injected in about 6 to 7 seconds Pause for 4 to 5 seconds 2. Inject remaining 20 to 25 c.c. solution at same rate as first portion	10 to 15 c.c.
Marked thrombosis, alternate method using 5-second exposure	Approximately 13 to 14 seconds	15 c.c.

*Note that with greater thrombosis the speed of injection is decreased. Much of the dye will be lost into the branches of the external and internal iliac arteries if strong force is applied when extensive femoral blockage exists.

producing local discomfort. No sloughing of the overlying skin has occurred. Injection of procaine is recommended to relieve the discomfort of the extravasated irritant.

TABLE III (B). SEQUENCE IN FEMORAL ARTERIOGRAPHY: OCCLUSION

	I	II	III
Minimal thrombosis	Rapid injection of 50 to 60 c.c. of 35 per cent Diodrast, requiring approximately 9 to 10 seconds*	Exposure started and in progress during rapid injection of approximately last 15 c.c.	
Moderate thrombosis	Injection at moderate rate of 50 to 60 c.c. of 35 per cent Diodrast, requiring approximately 11 to 12 seconds*	Exposure started and in progress during injection at moderate rate of approximately last 5 to 10 c.c.	
Moderate thrombosis alternate method	Injection at moderate rate of approximately 30 to 35 c.c. of 35 per cent Diodrast requiring about 6 to 7 seconds*	Pause for approximately 2 to 3 seconds	Completion of I with injection at same moderate rate of remaining 20 to 25 c.c. of 35 per cent Diodrast Exposure started and in progress during injection of last 10 to 15 c.c. in syringe
Marked thrombosis	As above*	Pause for approximately 4 to 5 seconds	As above
Marked thrombosis alternate method employing 5-second exposure	Moderate to slow injection of 50 to 60 c.c. of 35 per cent Diodrast, requiring approximately 13 to 14 seconds*	Exposure started and in progress during moderate to slow injection of approximately last 15 c.c.	

*Note that with greater thrombosis the speed of injection is decreased. Much of the dye will be lost into the branches of the external and internal iliac arteries if strong force is applied when extensive femoral blockage exists.

SUMMARY

A simple technique is outlined for obtaining satisfactory translumbar aortograms with simultaneous bilateral femoral arteriograms, and individual percutaneous femoral arteriograms. Standard equipment which may be found in the smallest hospitals is employed. No elaborate apparatus or special teamwork is necessary. The authors' personal experiences with a total of approximately 350 aortograms and arteriograms are the basis for this report. The method is described and illustrations of representative films are included. A valuable circulation-time test is recommended preliminary to percutaneous femoral arteriography. The incidence of complications has been remarkably low; possible explanations for this are considered in the course of the presentation. Remarks are made concerning the value and interpretation of aortograms and arteriograms.

TABLE IV (A). ARTERIOGRAPHY: POPLITEAL ANEURYSM

SIZE OF POPLITEAL ANEURYSM (APPROXIMATE DIAMETER)	DELAY BETWEEN FIRST PORTION (25 TO 30 C.C. OF 35 PER CENT DIODRAST) AND SECOND PORTION (25 TO 30 C.C. OF 35 PER CENT DIODRAST) OF INJECTION* (APPROXIMATE)
Small: 3 cm.	1 to 2 seconds†
Medium: 5 cm.	2 to 3 seconds†
Large: 8 or 10 cm.	3 to 4 seconds†

*At rapid rate if one or both pedal pulses palpable, but at slower rate if pedal pulsations absent.

†These pauses apply when one or both pedal pulses palpable. They should be at least doubled if no pedal pulsation is present.

TABLE IV (B). SEQUENCE IN FEMORAL ARTERIOGRAPHY: POPLITEAL ANEURYSM

	I	II	III
Small aneurysm	Injection of 25 to 30 c.c. of 35 per cent Diodrast*	Pause for approximately 1 to 2 seconds†	Injection of remaining 25 to 30 c.c. of 35 per cent Diodrast* Exposure started; in progress during injection of last 10 to 15 c.c. in syringe
Medium aneurysm	As above*	Pause for approximately 2 to 3 seconds†	As above*
Large aneurysm	As above*	Pause for approximately 3 to 4 seconds†	As above*

*At rapid rate if one or both pedal pulses palpable, but at slower rate if pedal pulsations absent.

†These pauses apply when one or both pedal pulses palpable. They should be at least doubled if no pedal pulsation is present.

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ADDENDUM

Since this paper was submitted for publication, there has been one anesthesia death at the Massachusetts General Hospital, from cardiac arrest following aortography.

To avoid a recurrence of this catastrophe, all aortograms performed in this institution under thiopental anesthesia are now carried out in the operating room with an inlying endotracheal tube and an intravenous muscle relaxant.

The technique, as presented in the body of this article, has been modified for the operating room cases. Because a portable machine is readily available in the operating room, it has been used to expose the film under the thighs in obtaining the simultaneous femoral arteriograms. The stationary x-ray tube has been employed for the abdominal film. Three-second exposures are used for both films. These are more satisfactory than two-and-one-half-second exposures. However, in the hospital radiology unit where aortograms and femoral arteriograms are obtained under local anesthesia, some of the technicians who are not experienced have difficulty in adjusting the machines available for exposures over two and one-half seconds. To keep the technical phase as simple as possible, for changing personnel and student technicians, the two-and-one-half-second exposure has been chosen for most of the aortography and arteriography performed on the hospital radiology floor.

In the operating room the abdominal film is taken in a grid cassette which is placed within a wooden tunnel on the operating table. The film beneath the thighs, resting on the table top, is in a regular cassette. For the abdominal film, 200 Ma. and approximately 75 kv. are employed. For the thigh films, 10 Ma. and 52 kv. (average) are used.

Because two x-ray machines are employed, a makeshift screen, consisting of a lead apron draped over a bar suspended between two infusion stands, is placed between the x-ray tubes to prevent fogging of the opposite films. The lower edge of the apron rests in the skin creases below the patient's buttocks. Cones are attached to the tubes to prevent scatter of rays. A portable shield for the aortographer is also used.

The same intervals between the abdominal and the femoral films are employed, as shown in the tables, depending on the extent of the artery occlusion.

Twenty-six aortograms have been performed by this method without difficulty, and excellent films of aorta and femoral arteries have been obtained.

As indicated in the text, aortography can frequently be carried out with ease under local anesthesia. Aortography is less painful than arteriography according to patients on whom both procedures have been performed separately under local anesthesia. If general anesthesia is chosen, the authors recommend insertion of an endotracheal tube by a skilled anesthetist, who has readily available all anesthesia equipment which may be needed.

To date, 595 aortograms and femoral arteriograms have been taken, with the death mentioned above being the only serious complication. Sixty-one aortograms have been obtained without femoral arteriograms, and 85 aortograms have been taken with 158 simultaneous femoral arteriograms of either one or both extremities. Two hundred and ninety-one femoral arteriograms have been carried out through the percutaneous route.

THE RETROGRADE FLUSH PROCEDURE IN EMBOLECTOMY AND THROMBECTOMY

E. STANLEY CRAWFORD, M.D., AND MICHAEL E. DEBAKEY, M.D., HOUSTON, TEX.

(From the Department of Surgery, Baylor University College of Medicine and the Methodist, Jefferson Davis, and Veterans Administration Hospitals)

EMBOLI may be removed successfully from most arteries at any point where they may be found except in the terminal peripheral branches and those at or inside the skull.[2, 5, 6, 7, 11, 13, 15, 16, 18] The limitations associated with embolectomy in the cerebral vessels are obvious and need no discussion here. In such peripheral arteries as the distal popliteal artery and its branches, repair of an arteriotomy and the accompanying spasm frequently produce sufficient constriction to impede blood flow and cause thrombosis. Under these circumstances, the operation fails to restore distal blood flow and consequently embolectomy is frequently withheld in these small but important occluded arteries.[18]

A second limiting feature of embolectomy is the high incidence of thrombosis that occurs proximal and distal to the obstructing lesion after a few hours.[9] For this reason it has been generally accepted until recently that, to be successful, operative treatment must be instituted within eight to fourteen hours of the accident.[3, 5, 9, 10, 12, 17, 18] In view of the frequency with which either the diagnosis is not suspected or the patient does not avail himself of treatment during this brief interval, the opportunity to re-establish normal circulation by simple embolectomy is often lost.

To overcome these limitations, numerous techniques have been advised or employed with varying degrees of success. In 1930, Lerman and associates[8] suggested that the distal arterial segment be flushed out with saline solution, and presented 2 cases in which such treatment was successful. Andrews and Harkins[1] reviewed the various methods of extraction of emboli that had been advocated up to 1932. These included use of probes, forceps, curettes, and catheters. They reported a case in which an embolus was removed from the iliac artery by insertion of a urethral catheter through a femoral arteriotomy and direction of it toward the iliac artery. Upon removal of the catheter, which fitted snugly to the arterial wall, a clot came into the wound and good blood flow into the thigh was established; however, absent distal pulses and color changes persisted until death of the patient a few days later. In 1941, Linton[9] described removal of an embolus and a part of the "tail clot" by retrograde milking or massage of the involved artery; blood flow was increased but apparently all the distal thrombus was not removed. Keeley and Rooney[4]

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suggested retrograde milking of an extremity by use of an Esmarch bandage, which is applied distally and wrapped toward the embolectomy arteriotomy, and they presented several successful cases. Recently, Olwin and associates[2, 11] reported successful removal of emboli and the distal thrombus by aspiration through a catheter or other instrument and in some instances by retrograde flush through a No. 5 ureteral catheter inserted well up into the posterior tibial artery. Shaw[14] successfully removed several emboli and thrombi by the retrograde flush technique.

In approaching these problems, we have employed several of the suggested techniques with some degree of success in all; however, with the exception of one method, much is to be desired. On two occasions the intima was injured while attempting to aspirate the clot and thrombosis promptly occurred at the site of injury causing the operation to fail. Milking or massaging the artery by any technique has frequently removed the obstructing clot or clots, but this has not been invariably true and some degree of distal obstruction has persisted.

In overcoming these limitations, we have obtained the most uniformly good results by employing the retrograde flush technique of Lerman and associates.[8] It is applicable to any peripheral artery at any level. The procedure consists in inserting a cannula into the artery distal to the disease and, through this instrument, forcibly injecting physiologic saline solution toward the embolus or thrombus or both. The clot is forced backward or upward to an opening which has been previously made in a segment of artery of sufficient size that repair can be accomplished without inviting thrombosis. A free flow of saline solution from the incision after the clot has been removed ensures an unobstructed lumen below. The single requirement of the procedure is a patent artery prior to embolization.

This maneuver has been highly successful in our experience, and in one instance, by adding it to the ordinary embolectomy operation, normal blood flow was re-established throughout an extremity five days after the accident. In view of this, and the report of Olwin and associates,[11] it is now our impression that the essential requirement for successful embolectomy, other than a previously patent vessel, is a viable part in the region supplied by the involved artery rather than opportunity expressed in terms of time.

A second problem in which this procedure has been most useful is thrombosis which occasionally occurs distal to the field of operation for other arterial lesions, such as aneurysms, trauma, or occlusive arteriosclerosis. On several occasions this additional maneuver has permitted a successful operation that would not have been possible otherwise. Amputation of a previously normal extremity, for example, has been prevented in at least five instances. In view of the gratifying results that we have had from application of this procedure in extending peripheral arterial operations and preventing disastrous complications in aortic operations, it seems worth while to present this experience in some detail as well as to describe our technique.

REMOVAL OF SMALL EMBOLI FROM THE DISTAL POPLITEAL ARTERY OR ONE OF ITS SUBDIVISIONS SUCH AS THE POSTERIOR TIBIAL ARTERY

The patient is placed in the lateral position with the involved leg down, slightly flexed at the knee. The uninvolved leg is flexed both at the hip and knee in order to remove it from the field of operation. An S-shaped incision is made behind the knee beginning medially over the distal end of Hunter's canal in the lower thigh and extending across the popliteal region ending below the knee between the two heads of the gastrocnemius muscle. The regional muscles and tendons are separated to expose the lower superficial femoral artery and upper popliteal artery (Fig. 1, *a*). The segment of artery

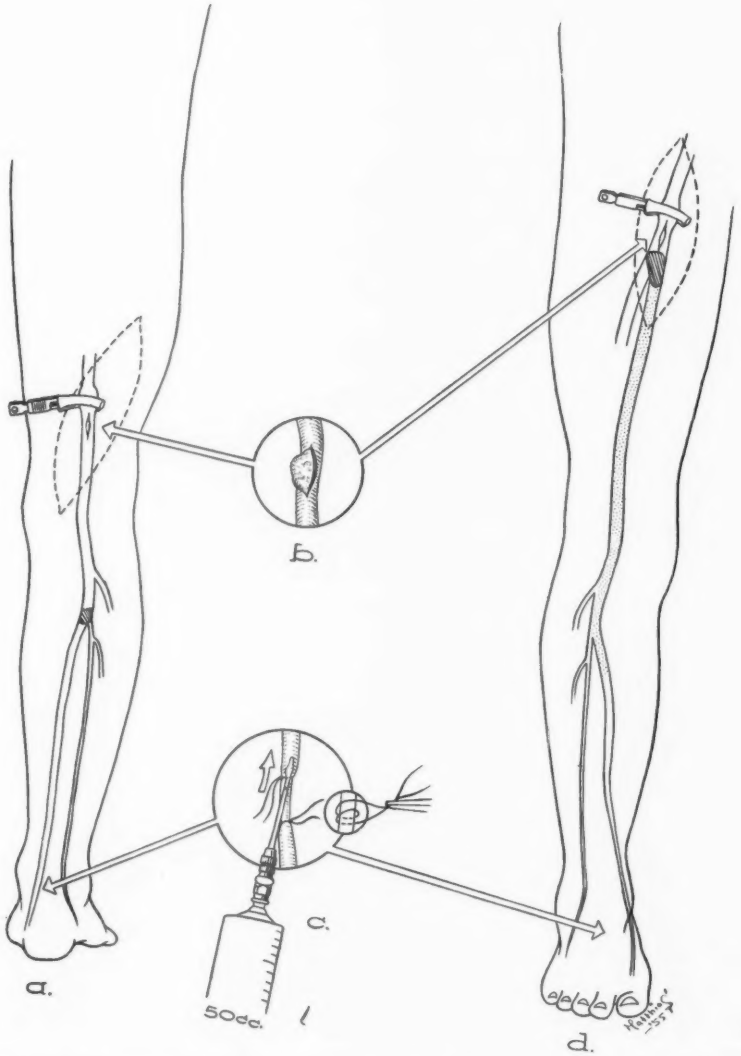

Fig. 1.—The major arterial system of the leg is diagrammed. An embolus is shown obstructing the distal popliteal artery in (*a*) and an embolus and its "tail clot" are obstructing the femorial artery in (*d*). Bleeding has been controlled by atraumatic clamps and short vertical incisions made distal to the clamps (*a* and *d*). A beaded cannula has been inserted as in (*c*) into the posterior tibial artery behind the internal malleolus (*a* and *d*). A 50 c.c. syringe containing warm saline solution is used to forcefully inject through the cannula (*c*).

with the largest diameter exposed is chosen for the arteriotomy. This is usually the lower femoral or upper popliteal artery. An atraumatic arterial clamp is placed above the region selected for embolectomy and a longitudinal incision is made into the artery. No clamp is placed distal to this incision and usually little retrograde bleeding occurs. The distal popliteal artery and its two terminal subdivisions, the posterior tibial and peroneal arteries, are exposed subcutaneously by blunt dissection with the index finger. Retrograde massage beginning over these distal arterial branches is carried out (Fig. 2).

Fig. 2.—The popliteal artery and its major branches are diagrammed. An embolus has obstructed the distal bifurcation of this artery. An atraumatic clamp has been applied and an arteriotomy made distal to it. A beaded cannula has been inserted as in Fig. 1, *c*. Retrograde massage of the artery prior to flushing has loosened and reduced the amount of clot.

Frequently a part or all of the clot is expressed from the lumen in this fashion. Should embolectomy or thrombectomy be complete by this maneuver, a brisk retrograde flow of blood will result; otherwise, the operation is incomplete. Nonetheless, the amount of clot is reduced and the remaining portion may be more easily removed by the following maneuver.

The posterior tibial artery is exposed behind the medial malleolus through a short transverse incision and is temporarily occluded distally. A small longi-

tudinal incision is made into the artery proximal to this occlusion and a beaded cannula is inserted toward the knee (Fig. 1, *c*). A temporary ligature occludes the artery around the cannula. A 50 c.c. syringe filled with physiologic saline solution is attached and emptied as rapidly and with as much force as is manually possible (Figs. 1, *a*, and *c*, and 2). Invariably, the remaining clot is flushed out of the arteriotomy in the upper wound (Fig. 1, *b*) and the profuse flow of clear saline solution which follows indicates a cleared segment between cannula and arteriotomy. The proximal arteriotomy is closed with a simple over-and-over 5-0 arterial silk suture and the proximal clamp is removed. The syringe immediately begins to fill with blood and upon removal of the cannula and temporary ligatures, brisk pulsatile hemorrhage ensues from the lower arteriotomy, which is closed with one or two interrupted 5-0 arterial sutures placed loosely in the adventitia.

REMOVAL OF AN EMBOLUS FROM A LARGER ARTERY AND THE DISTAL THROMBUS

Although this technique can be applied to an embolus and its distal thrombus at any location, it will be described as it applies to the femoral artery, in view of the frequency with which this artery is involved. An embolus usually obstructs the femoral artery at its bifurcation into superficial and deep femoral arteries because it is at this point that the vessel suddenly becomes smaller.

With the patient in the supine position, the common femoral artery is exposed through a small incision in the groin (Fig. 1, *d*). The location of the embolus is determined by the slight increase in the size of the artery which contains the clot, by the presence of a pulsation at and distal to the embolus only in the long axis of the artery instead of a normal expansile pulsation, and by palpation. Bleeding is controlled by applying an atraumatic arterial clamp only to the proximal segment. A small longitudinal incision is made into the artery over the embolus or slightly proximal to it. The embolus is milked out through this incision or lifted out with forceps. If thrombosis has not occurred distally, a brisk retrograde flow of blood will result which indicates patency of the artery distally. Under these circumstances, the arteriotomy can be closed with a simple over-and-over suture of 5-0 arterial silk. Pedal pulses will immediately become palpable. In rare instances, pulses are not felt beyond the popliteal artery; this indicates a second embolus at the bifurcation of this artery, which can be flushed out through either the femoral arteriotomy which is reopened or more easily through an incision in the proximal popliteal artery according to the technique described in the previous section.

If thrombosis had occurred beyond the embolus prior to operation, this would have become apparent by palpation at the time the artery was exposed. An artery containing a thrombus does not pulsate, and cannot be easily compressed without giving the sensation of containing solid material. In addition, upon removal of the embolus, free retrograde bleeding would not have occurred and local retrograde massage could have brought a part of the thrombus out of the arterial wound and into view. The thrombus is first reduced by retrograde massage of the leg and the remainder is flushed out through the

femoral artery by forcible injection of saline solution into the posterior tibial artery as already described (Figs. 1, *a*, *c*, and *d*, and 2). Occasionally, the clot is so adherent to the arterial intima that the flushing maneuver must be divided into two parts. In this situation, the popliteal artery is exposed and incised longitudinally. As much thrombus as possible is massaged from the artery through both incisions and then the remaining femoral arterial segment is flushed from the popliteal arteriotomy and cleared of the remaining clot. The distal segment is then cleared by massage and irrigation from the ankle upward as in the previous section (Figs. 1, *a* and 2). The arteriotomies are then closed and the occluding clamps removed.

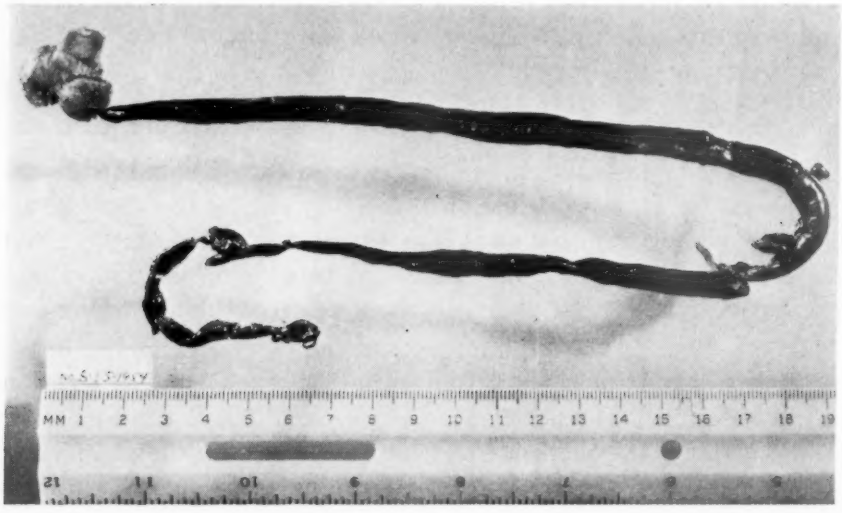

Fig. 3.—Photograph showing two of the cannulas and a screw attachment used to deliver saline solution into the posterior tibial artery.

REMOVAL OF A THROMBUS OCCURRING BEYOND THE REGION OF OPERATION OR INJURY

The artery is exposed in the region of the most distal palpable pulse which, in most instances, will be the femoral, popliteal, or in the event that the abdomen is open, the iliac artery. A longitudinal arteriotomy is made at this point and the distal artery is massaged toward the incision. This will draw the clot into the wound and frequently it can be removed completely by gentle traction, after which vigorous retrograde bleeding will result. In some instances, however, the thrombus will extend distally throughout most of the main arterial system and this maneuver will be inadequate. In such cases the thrombus, which is fresh and nonadherent, is easily flushed out by retrograde irrigation from the posterior tibial artery as previously described. On three occasions, a complete cast of the arterial tree distal to the common femoral artery has been removed and normal circulation has been re-established by this technique (Fig. 3).

CLINICAL MATERIAL AND RESULTS

This procedure has been employed in an attempt to restore normal arterial circulation in 11 consecutive patients (twelve extremities). Arterial

occlusion was due to emboli in 6 patients, thrombosis during operation in 3 cases, thrombosis proximal and distal to a thrombosed popliteal aneurysm in one case, and postoperative thrombosis in one case. The embolus was located in and beyond the distal popliteal artery in two extremities, at the bifurcation of the common femoral artery in 3 patients, and at the aortic, iliac, common femoral, and popliteal artery bifurcations in one patient. The duration of embolization prior to operation was five days in 2 patients, thirty-six hours in one, eighteen hours in one, and approximately two hours in the two extremities in which embolization occurred during operation. Thrombosis had occurred distal to the embolus and perhaps in some instances proximal to it as well in the four patients with embolization of greatest duration. Thrombotic occlusion occurred during operation in two extremities and in both was removed during the same operation. In the third patient, thrombosis occurred several hours after operation beyond an iliac homograft which became occluded by a piece of old thrombus from an unrecognized partially occluded aorta. Iliofemeropopliteal thrombosis occurred in association with suture line bleeding several hours after operation in the eleventh patient.

The major arterial channels in eleven of these extremities were cleared of the obstructing thrombus as evidenced by reappearance of pedal pulses. The operation was unsuccessful in one extremity containing an embolus and distal thrombus because of arteriosclerotic occlusive disease of the arteries in the lower leg proved by dissection of the amputated leg. In spite of palpable pedal pulses, amputation was performed in one of the 2 patients in whom embolization had occurred five days before operation. This patient had gangrenous changes in the toes before operation that did not regress after restoration of good pulses, and in spite of successful clearing of the arterial channels, there was a progressive necrosis of the calf muscles. Additional indications for amputation in this instance were pain and infection.

DISCUSSION

The retrograde saline solution flush maneuver has been added to the conventional operative techniques in twelve extremities to overcome the complicating factors of small arterial involvement and distal thrombosis. It is our opinion that the salvage of ten of these twelve extremities is attributed entirely to the addition of this procedure because such extremities have usually been lost previously in our experience. The free flow of clear saline solution from the upper arteriotomy has been a source of reassurance of a complete operation on more than one occasion.

Success in this small series of cases is due to an extremely important principle utilized in the technique and poor results are to be expected if this principle is not understood. It is essential that great intra-arterial pressure be produced between capillary bed or collateral bed and the obstructing clot in order to dislodge and flush out this obstructing lesion. It is therefore necessary to inject a volume of saline solution greater than the capacity of the artery to be irrigated and this must be delivered in the shortest possible time

and with a force considerably greater than the peripheral resistance offered by the capillary bed in order to prevent mere perfusion of the extremity. In our experience this has required a large bore cannula (Fig. 4), and a volume of 50 c.c. contained in and emptied from a single syringe. Rarely has more than one injection been necessary; therefore, the total volume injected has been small. A cannula with a beaded end has been preferred to that with a needle end because needles have frequently pierced the opposite arterial wall upon injection and the saline solution has been delivered outside the artery.

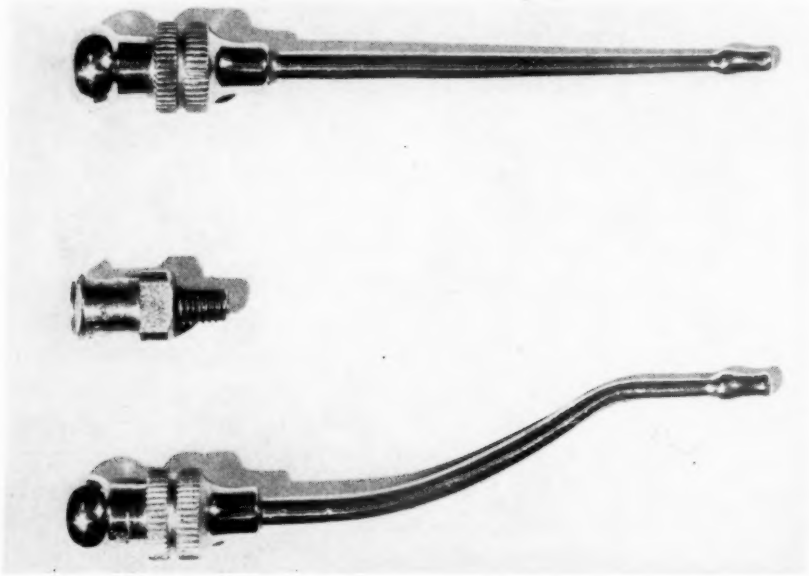

Fig. 4.—Photograph of a clot removed by the retrograde flush technique. Normal peripheral circulation was completely restored following its removal.

It is important that the artery be temporarily occluded around the cannula to prevent perfusion of the distal artery. The bead at the tip of the cannula has made this more successful. Instruments with small lumens, such as ureteral catheters, have been used with poor results. Pressure greater than that offered by the peripheral arterial resistance has been difficult to achieve because of the poor rate of flow through their small lumens, and limb perfusion has resulted. Furthermore, on two occasions, passing catheters into the lumen of essential arteries has resulted in intimal injury associated with thrombosis and failure to restore peripheral blood flow.

SUMMARY

During this era of more aggressive vascular surgery two complications of peripheral emboli continue to pose technical problems. The first is thrombosis distal to the occluding embolus. This complication is encountered not infrequently in view of the fact that its incidence increases after about eight hours of embolization. Under ordinary circumstances it is generally ac-

cepted that simple embolectomy beyond twelve to fourteen hours of the accident is unsuccessful in a relatively large percentage of cases because of this associated phenomenon.

A second complicating factor in the surgical treatment of peripheral emboli has been the size of the occluded artery. Repair of an opening in a small artery and the accompanying spasm have frequently produced sufficient constriction to impede blood flow and induce thrombosis. Under these conditions simple embolectomy has failed to restore distal blood flow often enough so that operation has been frequently withheld in small but important occluded arteries, such as the distal popliteal artery and its branches.

To overcome these problems the retrograde saline flush maneuver has been added to the usual procedure of embolectomy. When the embolus has been small and located in a small peripheral artery, an incision has been made in a segment of artery above the embolus where the size of the artery has been sufficient to permit repair without inviting local thrombosis. The embolus has subsequently been made accessible to this distant arteriotomy by flushing it backward with saline solution injected from a point in the artery distal to the embolus. Emboli in small distal popliteal arteries have been removed in this manner through an incision in the distal superficial femoral artery by exposure of the posterior tibial artery behind the ankle, insertion of a No. 14 beaded cannula into this vessel toward the obstruction, and injection of 50 c.c. of physiologic saline solution rapidly from a large syringe into the artery which has been temporarily occluded around the cannula. Often considerable pressure is necessary to dislodge the embolus and it is important to employ the largest possible cannula and to use a 50 c.c. or larger syringe because the delivered pressure depends upon volume and rate of flow. Ureteral catheters and other small instruments have been inadequate in producing pressure greater than that offered by the peripheral arterial resistance and local tissue perfusion has resulted.

Thrombi associated with an embolus have been removed by adding this maneuver to the usual embolectomy procedure. Thrombi that have occurred distal to arterial operations have been flushed out through proximal arteriotomies in the manner described for small emboli.

This procedure has been employed in 11 cases: six emboli, three intraoperative thrombi, one thrombosed popliteal aneurysm with thrombi both proximal and distal to the primary lesion, and one thrombus distal to a graft that thrombosed because of pressure from a hematoma. Thrombosis was also associated with 4 of the cases of embolism in which the time prior to operation had been from eighteen hours to five days. Normal circulation was completely restored and amputation prevented in 10 of the involved 12 extremities. Pedal pulses reappeared in another patient following removal of a femoral arterial embolus and the distal thrombus, but this was one of the 2 patients in whom embolization had occurred five days prior to operation and gangrenous changes had already occurred. Amputation was done because of progressive necrosis of the calf muscle, failure of regression of the gangrene in the foot, pain, and infection. The second failure occurred in a patient with

a femoral embolus and distal thrombosis. The distal thrombus was unsuccessfully removed by the retrograde flush maneuver because of the coexisting arteriosclerotic occlusion in the arteries of the calf proved by dissection of the amputated specimen. The only two limitations of this maneuver are therefore a previously occluded vessel between cannula and embolus or thrombus and a nonviable part distal to the embolus.

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PRIMARY MYCOTIC ANEURYSM

JOHN R. HANKINS, M.D., AND GEORGE H. YEAGER, M.D., BALTIMORE, MD.

(From the Department of Surgery, University Hospital)

THE term "mycotic" was adopted by Osler[15] to denote those aneurysms which originate on the basis of infection. In 1885, he reported a case in which both malignant endocarditis and aneurysms of the aorta were found at autopsy, and he postulated a common infectious origin for both the endocarditis and the aneurysms.

Eppinger[9] contributed much to the knowledge of the pathology of mycotic aneurysms, and showed that the dilatation of the vessel was dependent upon partial disintegration of its wall, especially the internal elastic lamina.

PATHOGENESIS

Stengel and Wolferth,[17] in reporting their collection of 264 mycotic aneurysms in 217 patients, provided an excellent classification of these lesions on the basis of their pathogenesis. The two major groups are:

Aneurysms of Extravascular Origin.—The causative infection extended to the vessel from a contiguous or neighboring inflammatory process outside its wall (for example, in tuberculous cavities, or the involvement of aorta or pulmonary artery by infection from bronchial lymph nodes).

Aneurysms of Intravascular Origin.—The initiating bacterial agent came from inside the vascular apparatus. These latter were further subdivided into three subtypes: (a) those developing from infected emboli which lodge in the vessel lumen or in the vasa vasorum; (b) those due to deposition of microorganisms directly on the intima of the vessel or in the vasa vasorum; and (c) those caused by extension of infection from aortic or pulmonic valves, in which case the proximal portions of the aorta and pulmonary artery, respectively, are involved.

Stengel and Wolferth stated: "In the development of mycotic aneurysms beyond the aorta and pulmonary artery, emboli usually play an important part." The source of the embolus is almost invariably an endocarditis, as sterile emboli have been productive of aneurysms only very rarely, if at all. The embolus serves the function of bringing the infection in contact with the vessel wall. Thus of 217 patients in their survey, 187 or 86.2 per cent showed evidence of endocardial disease. These embolic-mycotic aneurysms are usually found in locations where emboli are most likely to lodge, such as, bifurcations or areas where the lumen suddenly narrows.

In this discussion, we wish to draw particular attention to those aneurysms in which there is no associated endocarditis or emboli (Type II-b). Crane[6]

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originated the term "primary mycotic aneurysm" to apply to those arterial lesions not associated with any demonstrable intravascular inflammatory focus, such as bacterial endocarditis, or with any in the surrounding tissues. Revell[16] could find only 23 cases of this type reported in the literature, and to these he added a case of his own. He theorized that the most likely mode of infection of the aorta is through the vasa vasorum because "the volume and velocity of blood flow through the aorta would not favor the lodgement and development of bacteria on an undamaged intima." However, in more peripheral arteries this would not necessarily be the case. Direct infection of the intima of an artery during the course of bacteremia is considered very rare, as intact intima is quite resistant to infection. Some workers have felt that the intimal defects caused by arteriosclerosis may allow the infection to gain a foothold. To substantiate this assumption, mycotic aneurysms have been reported which were found in the midst of arteriosclerotic patches. Certainly in one of the two cases herein reported, this is a very likely sequence of events, as the patient had evidence of generalized arteriosclerosis.

PATHOLOGY

Grossly, these lesions have no characteristic shape and are usually small when compared to those of syphilitic origin.

In those of embolic origin, the arterial tree, apart from the aneurysm itself, is usually intact and, as one approaches the aneurysm, there is a sudden transition from normal artery to the lesion.

The natural history of the lesion depends on the virulence of the inflammatory agent causing it. If the agent is of a high degree of destructiveness, the entire arterial wall disintegrates and rupture takes place before any dilatation has had time to occur. Thus a false aneurysm results if the accident occurs in a peripheral artery. In more subacute types of inflammation, there is more likely to be some dilatation of the lumen as a result of dissolution of the elastic fibers, but there may also be evidence of reparative processes, and a thickened fibrous wall may form. Microscopically, the intima is sometimes found growing down from the surrounding normal artery into the sac, but it never lines the interior completely while active inflammation is still in progress. Rupture may never occur and complete healing may take place, in the case of peripheral arteries by thrombosis and eventual obliteration of both the sac and the arterial lumen.

In embolic-mycotic aneurysms one usually finds an inflammatory reaction in the vessel wall which corresponds, in degree, to that in the heart valve. On the other hand, in the case of those nonembolic aneurysms associated with bacteremia (primary mycotic), the inflammatory process is usually acute, and rapid destruction of the arterial wall, with perforation, occurs. Microscopically, there is marked infiltration of polymorphonuclear leukocytes into the area, and abscesses of the vessel wall are often found.

BACTERIOLOGY

In two of the larger collections of cases published in the literature (Lewis and Schrager,[13] and Stengel and Wolferth[17]), both of which deal primarily

with embolic-mycotic aneurysms, the streptococcus was, as would be expected, the organism most commonly found. Staphylococci and pneumococci were found in fair numbers, and the influenza bacillus and gonococcus in a few instances. In Revell's[16] study of the primary mycotic aneurysms, pneumococci and streptococci were present in 6 cases each, these being followed in incidence by the gonococcus and then the staphylococcus.

Cathcart's[3] case of a femoral aneurysm occurring during the course of typhoid fever has been considered as probably being mycotic, but he failed to provide satisfactory proof that this was a true mycotic aneurysm due to typhoid bacillus infection.

The only bona fide case of mycotic aneurysm associated with a Salmonella infection which could be found in a search of the literature was that reported in a clinicopathologic conference at Massachusetts General Hospital.[4] This was a ruptured aortic aneurysm ending in a fatality; *Salmonella typhimurium* was found on blood culture, and clumps of bacteria were also found in the aortic defect. Weller[19] reported a fatal case of ruptured aortic aneurysm associated with a bacteremia due to *Salmonella choleraesuis,* var. *Kunzendorf.* However, the aneurysm, on microscopic examination, proved to be arteriosclerotic and not mycotic. Our case apparently is the second case on record of mycotic aneurysm due to Salmonella.

CLINICAL ASPECTS

The sex incidence in mycotic aneurysms in general reveals that males predominate over females in a ratio of well over two to one. The peak age incidence, which is determined by the age incidence of the underlying diseases, is primarily in the third and fourth decades. Revell's series did not differ materially from those series dealing primarily with embolic mycotic aneurysms in respect to sex and age incidence.

In regard to anatomic location, unfortunately the aneurysms peripherally located and readily accessible to early diagnosis and successful attack are in the minority. Lewis and Schrager[13] found the lesion located in a peripheral vessel in only 23 per cent of the cases. The superior mesenteric artery was the most common site, followed by the cerebral arteries, aorta, and femoral artery. Stengel and Wolferth[17] found the vessels of the extremities involved in only approximately 20 per cent of the cases. The aorta was the most frequent location in this series, followed by the superior mesenteric and hepatic arteries. Revell, on the other hand, found that out of 28 aneurysms occurring in his 24 cases, the aorta was involved in 20 of them. The only peripheral vessel attacked in his series was the femoral artery (one instance); although the subclavian was involved in two instances. The incidence of multiple aneurysms occurring in the same patient, is, as would be expected, somewhat higher in the embolic series.

Clinically, mycotic aneurysms are characterized by rapid evolution. Sometimes rupture occurs within a week or two of the beginning of symptoms. More commonly, rupture, if it occurs at all, takes place only after symptoms have been present for several weeks.

Unfortunately, in the case of internal vessels (thoracic and abdominal), rupture often occurs and ends fatally before the aneurysm has reached a large enough size to be detected clinically. It is in peripheral or superficial lesions that the best opportunity for early diagnosis is afforded, as, in typical cases, a characteristic pulsating tumor appears a few days after the impingement of the inflammatory agent on the vessel wall. Sometimes pain in the area precedes the development of the swelling, and these cases may be erroneously diagnosed as phlebitis or arthritis.

When frank rupture occurs, the swelling suddenly becomes more painful and tense. Even false aneurysms, however, may retain expansile pulsation. There is usually absence of pulse with evidence of circulatory impairment in the extremity distal to the aneurysm, but gangrene is rather uncommon. In the case of the embolic-type aneurysm, the diagnosis is made somewhat easier by the fact that usually there has been an episode of known endocarditis preceding, or even concurrent with the development of the vascular lesion. With nonembolic aneurysms the course is different. There may be a history, or evidence at the time, of an infectious process elsewhere in the body, such as otitis media or pneumonia. On the other hand, there may be only a "fever of unknown origin" preceding the development of the lesion, as in one of the cases being presented in this report.

CASE REPORTS

CASE 1.—E. H., a 76-year-old white woman, was admitted to the medical service on Aug. 5, 1953, with a tentative diagnosis of rheumatoid arthritis. She was a known mild diabetic, and had had various joint aches and pains of an ill-defined nature for the preceding seven months. Her symptomatology had become more marked three days prior to admission, and two days prior to admission her right knee had become hot and swollen. Physical examination revealed an acutely ill, elderly person, somewhat lethargic and confused, with a temperature of 103° F. The skin was hot and dry, and there were eye-ground changes consistent with arteriosclerosis. The chest revealed moist râles in the right base. The heart was not remarkable and no murmurs were heard. There was marked swelling, tenderness, and local heat on the medial aspect of the right thigh just above the knee. This area was firm on palpation. There was also slight generalized swelling of the entire right lower extremity—the calf measurements being 12⅞ inches on the right as compared to 11½ inches on the left. Good femoral pulsations were felt bilaterally but the presence of dorsalis pedis pulsations, bilaterally, was questionable. There was no posterior tibial pulse felt on either side. Homan's sign on the right was equivocal.

Hospital course: The patient was given general supportive therapy, and on the day following admission, penicillin was begun (after a blood culture had been drawn). The admission laboratory data showed a negative serologic test for syphilis; hemoglobin 58 per cent; leukocytes 6,300, elevated to 26,000 the day after admission. The electrocardiogram showed only sinus arrhythmia and occasional ventricular premature beats. Chest roentgenogram showed no significant changes. However, hypertrophic changes in the right shoulder, and changes in the joints of the hands, compatible with rheumatoid arthritis, were revealed by roentgenography. The blood sugar was never above 250 mg. per cent during the entire hospital course. Urinalysis showed one-plus albumin, and sugar on occasion. Because of the possibility of a phlebitis, the patient was begun on Depo-heparin and Dicumarol therapy on August 7, two days following admission. On this same date, intramuscular penicillin was discontinued and oral Chloromycetin begun. The diabetes was easily controlled on small daily doses of NPH insulin. Dicumarol was continued in small doses until August 11, and, when discontinued on August 12, the prothrombin time was 51 sec. -10 per cent.

During the first five days of her hospital course, the tender area above the right knee gradually became more erythematous and fluctuant, and a necrotic bleb developed over it. The patient ran a spiking temperature elevation up to 102.8° F., which tended to come down after starting Chloromycetin therapy. On August 12, because of the fluctuant nature of the local condition, the patient was taken to the operating room where incision and drainage were performed. A large amount of "bloody pus" was obtained and Penrose drains were inserted. Due to the extremely superficial "pointing," the drainage incision was definitely not carried deep enough to have injured any major vessel. The source of the inflammatory process could not be definitely ascertained. However, a culture of the drainage, taken at the time of operation, yielded *Salmonella choleraesuis*, var. *Kunzendorf* in heavy growth. At this time, the blood culture drawn on August 6 was reported as having grown out the same organism, and the same result was reported on the blood culture drawn on August 12.

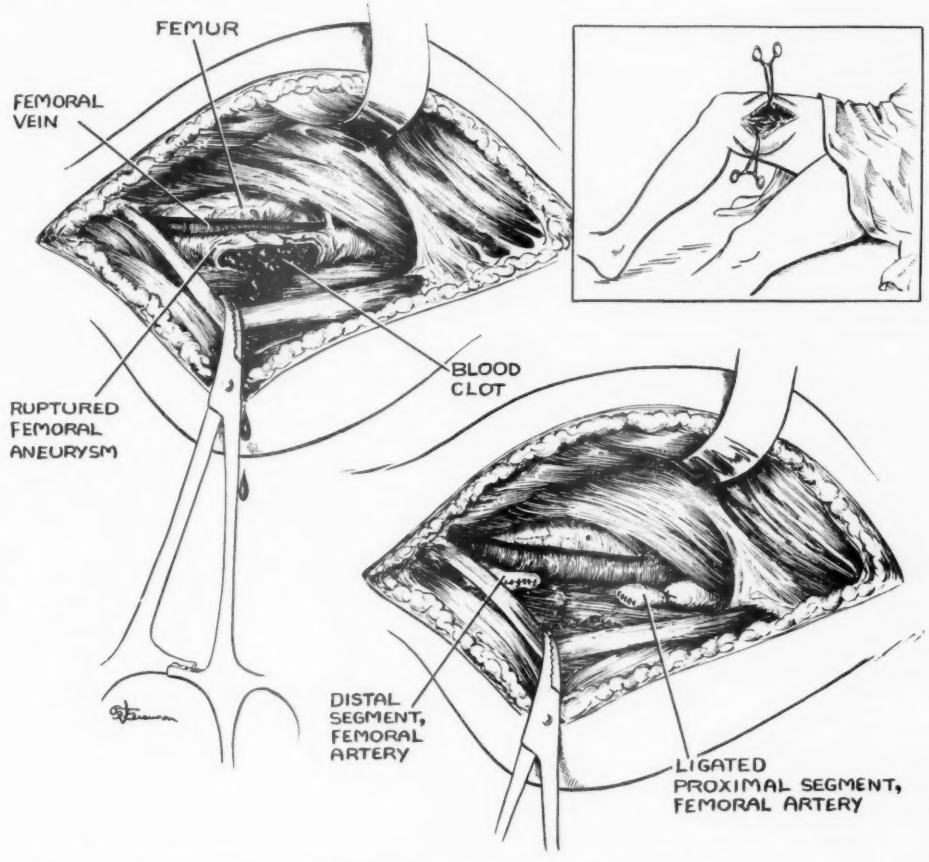

Fig. 1.—Ruptured femoral aneurysm in Case 1.

The patient was continued on Chloromycetin, to which this organism was shown to be sensitive. However, the local area on the right thigh continued to enlarge, and the whole lower thigh became quite tense. The drainage incision slowly oozed thin bloody fluid. On August 20, because of fairly free oozing, she was taken to the operating room and, after anesthesia and draping, blood clots presenting in the drainage incision were evacuated. Immediately, a large amount of arterial blood gushed forth in a steady spurt. The incision was enlarged and tourniquets were placed around the extremity above and below the incision. The operator then sutured, with 5-0 silk, what was thought to be a tear in the femoral artery. When all bleeding had been stopped, the tourniquets were removed. It was then possible to identify structures accurately. It was found that the femoral artery, at a point just above the popliteal space, had completely fragmented, or disintegrated, in

an area approximately 2 cm. in length (Fig. 1). The femoral vein was intact. The fine silk sutures, which at first were thought to have simply closed a tear in the artery, were now seen to be completely closing the ragged, free proximal end of the vessel. Because this closure seemed somewhat precarious, a ligature of 0 chromic catgut was placed around the artery proximally for added protection. The distal end of the artery was not bleeding, and, since it was difficult to delineate in the necrotic mass, it was left alone. After

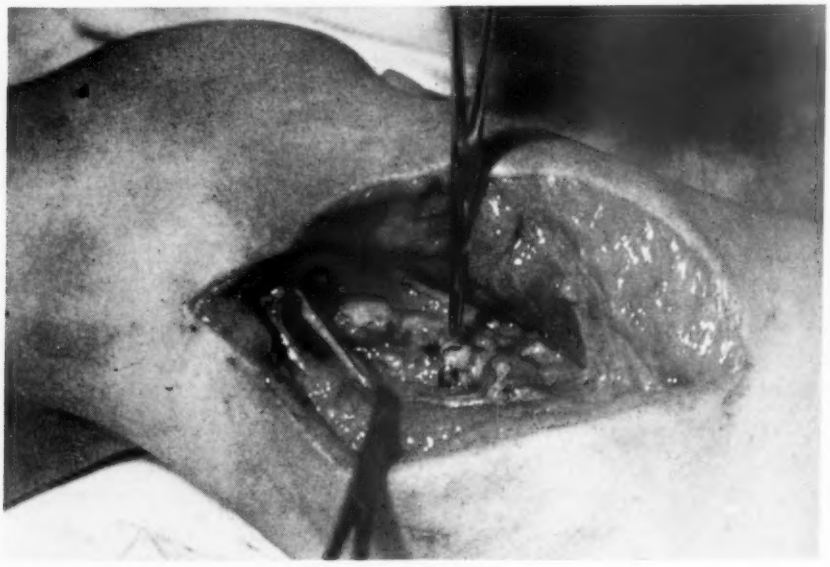

Fig. 2.—Wound two days postoperatively. Upper clamp points to proximal ligated end of artery.

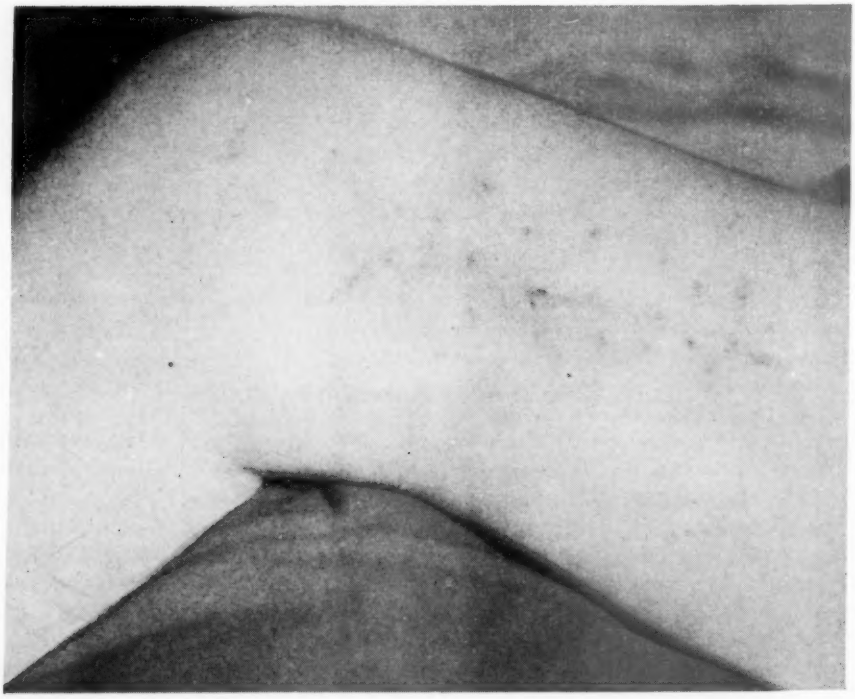

Fig. 3.—Healing wound after secondary closure.

considerable necrotic tissue and clots had been removed, the wound was found to be extensively undermined and a goodly portion of the femur was exposed. The wound was left open and packed with petrolatum gauze (Fig. 2).

Cultures of the wound taken at the time of operation, and again as late as October 17 (four weeks postoperative) continued to show *Salmonella choleraesuis*, var. *Kunzendorf*. Following ligation there were only transient signs of ischemia in the right foot, and, within a day or two, this foot was as warm, if not warmer, than the left foot. Chloromycetin was continued, and the packing was gradually removed from the wound. With daily irrigations, granulation tissue gradually filled the wound. Secondary closure of the wound was carried out on October 17 (Fig. 3), and the patient was discharged from the hospital on October 29 with the wound healed.

When last seen several months later, the patient had an adequate circulation to the right lower extremity and walked with only a slight limp.

Comment.—In recapitulating the course of events, this patient's illness undoubtedly began with a Salmonella bacteremia, the organism probably entering through the gastrointestinal route. There were no gastrointestinal symptoms, but absence of these is not uncommon with this particular type of Salmonella. Apparently the first, and only, place the infection localized was in the femoral artery, probably on an arteriosclerotic plaque. There was certainly no clinical evidence of endocarditis. The infection in the artery rapidly led to rupture with formation of a false aneurysm. Admittedly, the ill-advised use of Dicumarol may well have hastened this process by preventing clotting, the diagnosis not being suspected at the time of its use. Unfortunately, it was not feasible to obtain a biopsy of the vessel wall in this case.

Case 2.—C. K., a 75-year-old white man, was admitted to the surgical service on May 26, 1945, because of a mass behind the right knee of about one year's duration. His history was not too clear, but he stated that approximately one and one-half years previously he had felt "something snap" in his right calf after working in a squatting position for several hours. Since that time, he had not been able to squat for long periods of time without experiencing pain in the calf. In April, 1944, he had been hospitalized in another hospital with a severe attack of pneumonia. While convalescing from this, he had noticed a lump forming behind his right knee. Physical examination revealed a man who looked younger than his stated age of 75. Inspiratory wheezes were heard in the hilar area of the right lung, but except for this the only physical finding of note was a pulsating, nontender mass the size of a hen's egg in the right popliteal region. It showed no signs of inflammation, and no bruit could be heard. Pulsations disappeared when the femoral artery was occluded by proximal pressure.

Chest roentgenogram revealed moderate cardiac enlargement and a probable aneurysm of the descending aorta. The serum flocculation test for syphilis was negative on one occasion but positive on another. The leukocyte count on admission was 18,000 but other laboratory studies were not significant.

Within several days following admission, the mass gradually became larger and the extremity below the aneurysm became cold, swollen, and edematous. He complained of considerable pain in the leg; hence, amputation just above the knee was carried out on June 4. The pathologic examination of the specimen revealed many blood clots in the popliteal fossa, and when these were expressed, an aneurysmal sac about 10 to 15 cm. in circumference and about 4 cm. in length was revealed. The surrounding tissue was indurated. Microscopic examination showed "portions of vessel wall or aneurysmal sac with scarring, inflammatory infiltration, and calcification in the wall. The surrounding fatty and muscular tissue shows a heavy leukocytic infiltration. Organizing thrombi are also present." The impression was mycotic aneurysm (Fig. 4). The amputation stump healed satisfactorily and the patient was discharged on June 20.

Comment.—Many features of this case seem to point to an arteriosclerotic origin of the aneurysm rather than to a mycotic one, but the pathologic report gives incontrovertible evidence of the latter. It is conceivable that an arteriosclerotic aneurysm might have become secondarily infected through bacteremia from the pneumonia. The pain in the right calf, if the history is accurate,

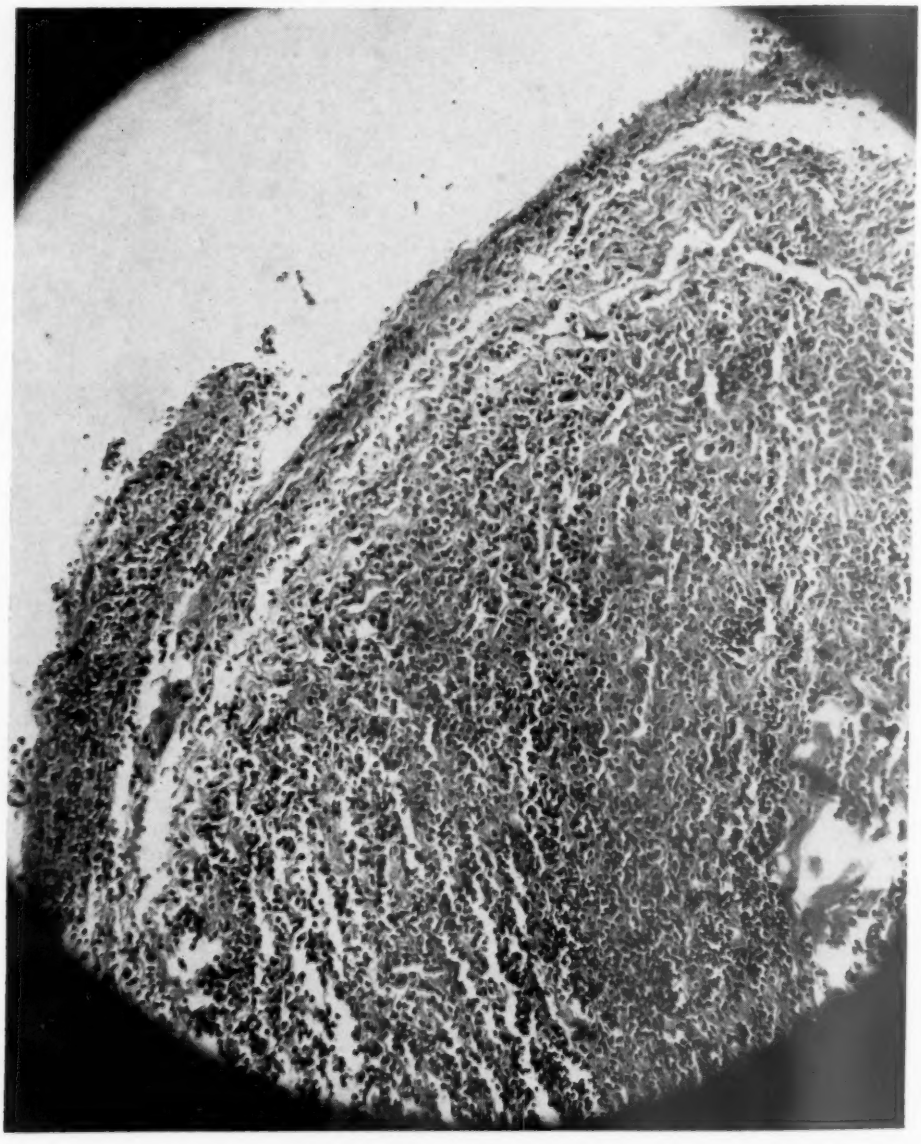

Fig. 4.—Photomicrograph (low power) of aneurysm wall in Case 2 showing leukocytic infiltration.

antedated the pneumonia, although the swelling did not. The many clots in the popliteal area found on examination of the amputated extremity makes one wonder if rupture had already occurred, but this is not clear from the report. Certainly if this man had come for surgical treatment earlier, the aneurysm might have been excised, and the extremity saved.

DISCUSSION

Most authors writing before the era of antibiotics were quite pessimistic about the outlook of surgical treatment of mycotic aneurysms because the patients usually died of the underlying infection, or developed more aneurysms, even if the initial one was attacked surgically. In Lewis and Schrager's day (1909) the longest period of time that a patient had survived following operation for embolic-mycotic aneurysm was seven months.

Since the advent of the antibiotic era, a more optimistic view is justified. The underlying endocarditis or bacteremia can be resolved by antibiotics in a large percentage of cases. However, even now mycotic aneurysms sometime manifest themselves after the underlying endocarditis has been pronounced as cured, due to implantation of bacteria on the vessel wall before the antibiotic effected sterilization of the blood stream. In most of these cases, as Hurwitz and Arst[12] point out, the aneurysm is found to be sterile at operation. On the other hand, Cates and Christie[2] maintain that infection may persist in the aneurysm even though it has been eliminated from the heart valve.

Barker[1] recently reviewed the cases of successfully treated mycotic aneurysms and was able to find only 10 cases, to which he added a case of his own. Of the 11 patients, only 9 received surgical treatment (4 had ligation alone, 3 excision alone, and 2 a combination of the two methods). Nine out of the 11 patients were in some way related to subacute bacterial endocarditis (8 directly, and the ninth was due to bacterial endaortitis which developed in association with a coaretation, the patient also having an arrested subacute bacterial endocarditis).[14] Two of the 9 patients later died of subacute bacterial endocarditis. Thus, only two of the aneurysms reported by Barker could be said to be primary mycotic; one showed spontaneous thrombosis and cure after penicillin and sulfamerazine treatment,[11] and the other was a femoral aneurysm which occurred in an elderly patient following pneumonia.[5] This was treated by ligation and drainage, and a cure resulted after suppuration.

To the 11 cases collected by Barker can be added the case of an aneurysm of the superior mesenteric artery associated with subacute bacterial endocarditis cured by excision, reported by DeBakey and Cooley[7]; that of Demirleau and Corcos,[8] a femoral aneurysm in a pregnant female following therapy of endocarditis, treated by endoaneurysmorrhaphy under direct aortic compression; that of Germer and Fischer,[10] resection of an aneurysm of the common iliac artery; that of Trisidder and Warren,[18] bilateral aneurysms of posttibial artery treated successfully by excision; and that of the authors (Case 1).

Barker indicates that, at the present time, excision of the aneurysm where possible is the procedure of choice. Excision is undoubtedly the wisest course of action for an aneurysm having a well-defined sac. In cases such as ours (Case 1), however, there is nothing to excise, and proximal ligation is necessary to prevent exsanguination. Even in these rapidly developing aneurysms there is apparently enough time for collateral circulation to develop so that the distal extremity survives when the main artery to the extremity is ligated.

SUMMARY

The pathogenesis, pathology, bacteriology, and clinical aspects of mycotic aneurysms of intravascular origin are presented. A distinction is drawn between the more common embolic-mycotic aneurysms associated with endocarditis, and the rarer primary mycotic aneurysms which are not associated with demonstrable intravascular or adjacent inflammatory foci.

Two illustrative cases of primary mycotic aneurysm of the lower extremity are presented: one associated with Salmonella bacteremia and treated successfully by proximal femoral ligation; the other followed a case of pneumonia and was seen too late for successful treatment. The former was only the second case that could be found in the literature of a mycotic aneurysm resulting from Salmonella infection.

Treatment of these aneurysms is discussed. Excision is felt to be the treatment of choice in those lesions which have a definite sac, but, in rapidly developing lesions, no sac may be present and ligation proximal to the aneurysm is the procedure that is indicated.

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INTRAPERICARDIAL ASBESTOS IN EXPERIMENTAL CORONARY ARTERY LIGATION

P. G. Grice, M.D., R. W. Rodrigues, M.D., H. Kajikuri, M.D., A. Riberi, M.D., and H. B. Shumacker, Jr., M.D., Indianapolis, Ind.

(From the Department of Surgery, Indiana University School of Medicine)

THE intrapericardial application of irritative substances has been studied extensively with regard to possible protection against coronary artery ligation.[3, 5, 7, 11-13] One material reported to be effective is asbestos. The present study was undertaken to learn whether spreading shredded asbestos over the epicardium would alter the mortality from division of the left anterior descending coronary artery. Other studies from this laboratory permit us to compare the results of this effort with those in animals with ligation of the great cardiac vein, those in untreated controls, and in those in animals having had simple pericardiotomy as an operative control.[9]

MATERIALS AND METHODS

Healthy mongrel dogs weighing between 6.8 and 17 Kg. were used. Anesthesia was induced by the intravenous administration of sodium thiopental. Tracheal intubation was accomplished and an oxygen-ether mixture was given by means of a mechanical respirator. Aseptic technique was followed. A thoracotomy was performed through the left fifth intercostal space. An incision was made in the pericardium in a crescent or "U" shaped manner around the border of the left auricular appendage, care being taken to avoid injury to the phrenic nerve (Fig. 1). This pericardial flap was then sutured to the epicardium with 5-0 Atraumatic arterial silk in an attempt to isolate the area of origin of the anterior descending branch of the coronary artery from the pericardial cavity and thus from irritation by the asbestos to be applied. From 0.15 to 0.25 Gm. of sterile shredded asbestos were then placed in the remaining pericardial space and spread as evenly as possible over the epicardial surface. The free edge of the pericardium was sutured to the epicardium with 5-0 Atraumatic arterial silk. The pleural cavity was irrigated with saline, the lungs were expanded and the chest closed in layers.

All dogs were allowed to recover from this procedure and ligation of the coronary artery was carried out one month later through a thoracotomy in the left fourth intercostal space. At this time the "isolated" pericardial space was entered and found relatively free from adhesions. Any adhesions encountered were filmy and did not bleed when disrupted. The left anterior descending coronary artery was divided between two 3-0 silk ligatures. The proximal ligature was placed as nearly flush with the origin of the left anterior descending branch as possible. Care was taken to insure adequate oxygenation during this procedure. If the animal did not die immediately, the lungs were expanded fully and the chest wall closed.

All hearts were carefully examined at the time of death or sacrifice to confirm the level of division and to determine whether or not the septal coronary artery was also occluded by the ligature. The presence of infarction was noted. The exact extent of infarction involving the epicardial surface could not be determined accurately because of the firm fusion with the overlying pericardium.

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Measurements of peripheral coronary artery pressure, flow, and estimation of intercoronary communications by the injection technique of Schlessinger[8] were carried out in 10 dogs. These were divided into two groups of 5 each, one studied immediately after, and the other 24 hours after, ligation. Retrograde pressures were measured by means of a polythene tube placed in the artery just distal to the point of ligation and attached to a strain gauge manometer. Immediately after satisfactory pressures were recorded, retrograde flow was measured by collecting in a graduated cylinder the blood flowing from the tube during a unit of time. The open end of the polythene tube was kept level with the ligated artery during this study.

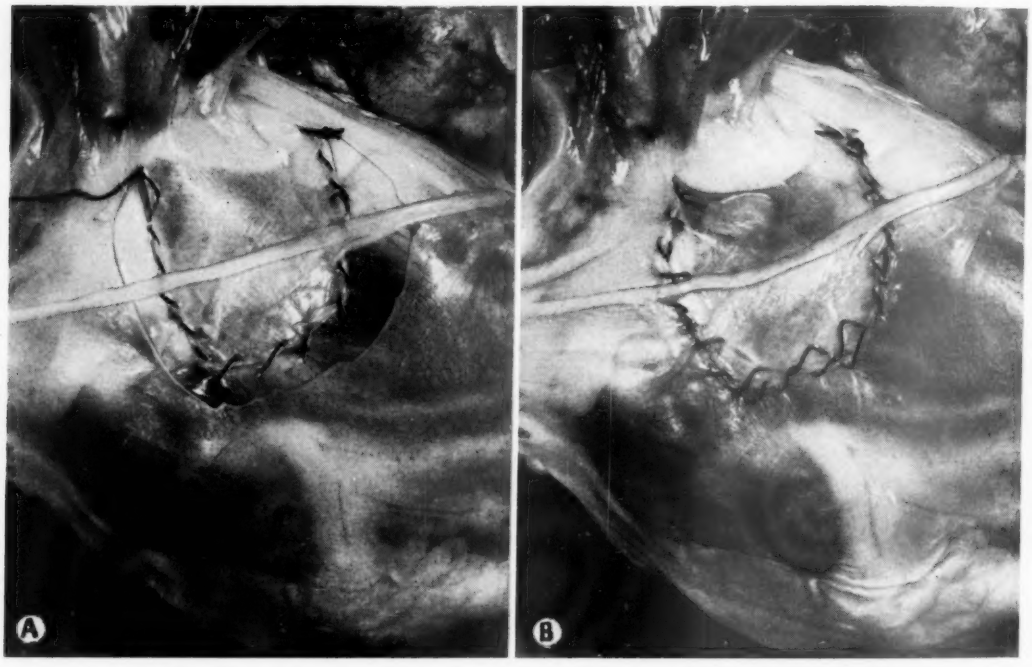

Fig. 1.—Photographic illustration of the incision in and suture of the pericardium utilized to prevent adhesions from forming in the region where subsequent ligation of the left anterior descending coronary artery is accomplished (*A*), and closure of pericardial sac after insertion of asbestos (*B*). The suture used for purposes of illustration is larger (2-0) than that actually employed in the experiments.

No separate control group was studied in this investigation since we have made adequate control observations in this laboratory.[4, 9, 10] In these control studies the arterial division was performed in precisely the same manner as that described for this experimental group. Most of the untreated control group were operated upon through a left fourth intercostal incision. Some were performed through a bilateral anterior thoracotomy. There was no significant difference in the mortality regardless of the type of incision.

RESULTS

Of 20 dogs with successful ligation and division of the coronary artery, 11 survived a period of thirty days and 9 died, an over-all mortality of 45 per cent. Most of the dogs which died did so within twenty-four hours, although one lived as long as three days. Dissection of the coronary arteries revealed the fact that 13 of these dogs had their septal artery occluded by ligation of the left anterior descending coronary artery. Thus the mortality was 14 per cent in dogs with occlusion of only the anterior descending artery, while in dogs in which the septal artery was also occluded it was 61.5 per cent. In contrast, the mortality in nearly 50 control dogs without occlusion of the

septal artery was 57.5 per cent, and it was 100 per cent whenever the septal artery was occluded in addition (Table I). Infarcts were noted in all dogs sacrificed and they averaged about 2.5 cm. in diameter. Because of the overlying adhesions it was difficult to ascertain whether or not all were through-and-through infarcts, though it was our opinion that some were not.

TABLE I. MORTALITY FROM LIGATION AND DIVISION OF THE LEFT ANTERIOR DESCENDING BRANCH OF THE CORONARY ARTERY

PROTECTIVE PROCEDURE	ANIMALS WITH PATENT SEPTAL ARTERY	ANIMALS WITH OCCLUDED SEPTAL ARTERY
Asbestos	1 of 7 (14.3%)	8 of 13 (61.5%)
Great cardiac vein ligation	1 of 8 (12.5%)	3 of 4 (75%)
Pericardiotomy	6 of 22 (27.3%)	6 of 10 (60%)
None (controls)	27 of 47 (57.5%)	12 of 12 (100%)

Studies of peripheral coronary pressures measured immediately after ligation revealed a range between 36/24 and 102/20 mm. and an average of 55/17 mm. In those studied 24 hours after ligation, the range was from 40/20 to 74/30 mm., averaging 62/26 mm. Retrograde coronary flows in the group measured immediately after ligation varied from 0.3 to 10.0 c.c. per minute with an average of 2.6 c.c. per minute, while in dogs ligated 24 hours previous to measurement, they varied from 1.6 to 6.0 and averaged 3.0 c.c. per minute (Table II). Injection studies did not seem to show any difference in intercoronary communications when carried out immediately and 24 hours after ligation.

TABLE II. RETROGRADE PRESSURE, FLOW, AND INJECTION STUDIES

STUDIES MADE IMMEDIATELY AFTER LIGATION				STUDIES MADE 24 HOURS AFTER LIGATION			
DOG. NO.	RETROGRADE FLOW IN C.C./MIN.	DISTAL ARTERY PRESSURE IN MM. HG.	DISTAL ARTERY FILLING ON INJECTION STUDY*	DOG. NO.	RETROGRADE FLOW IN C.C./MIN.	DISTAL ARTERY PRESSURE IN MM. HG.	DISTAL ARTERY FILLING ON INJECTION STUDY
ASBESTOS-TREATED ANIMALS							
80	1	48/17	++	93	6	74/30	++
81	1	40/10	0	95	2.4	66/20	+
82	10	102/20	+++	96	2.4	40/20	0
85	1	50/12	0	98	1.6	72/35	+
108	0.3	36/24	0	107	2.4	60/24	0
Average	2.7	55/17		Average	3.0	62/26	
GREAT CARDIAC VEIN LIGATION							
Average	1.1	42/13		Average	3.2	62/19	
PERICARDIOTOMY							
Average	1	34/14		Average	3.8	47/18	
UNTREATED CONTROLS							
Average	1.5	32/10		Average	1.0	43/15	

*The same method of grading results of injection studies was used as in reference 7: 0, no evidence of filling distal to ligature; +, presence of contrast material though scattered; ++, complete filling though not of as large caliber as rest of coronary tree; +++, complete filling distal to ligature and of equal caliber to the remaining coronary tree.

In one exceptional dog studied right after ligation, the distal coronary pressure was 102/20 mm., the retrograde flow was 10.0 c.c. and the injection studies revealed excellent intercoronary communication. These values were very much greater than in the other 4 animals in this group and are attributed to the presence of unusual intercoronary communications. If data from this

dog were excluded, the average pressure immediately after ligation would be 43.5/16 c.c. and the average flow 0.9 c.c. per minute. The pressure, flows, and filling of the distal segment would then be greater in the group studied 24 hours after ligation.

Of 48 dogs in which asbestos was placed in the pericardium, 12 developed a cystlike collection of a serosanguinous fluid in the region over the right ventricle (Fig. 2). Such cysts were entirely surrounded by a dense ring of asbestos and adhesions. In all such cases the rest of the pericardium was firmly attached to the epicardium. In one dog there was a cyst located over the upper part of the right ventricle but not completely covering the atrioventricular ring. This dog did not develop clinical evidence of right heart failure. The other 11 had cysts compressing the right atrioventricular ring. They all had ascites, pleural effusion, or both. Eight of them died in heart failure.

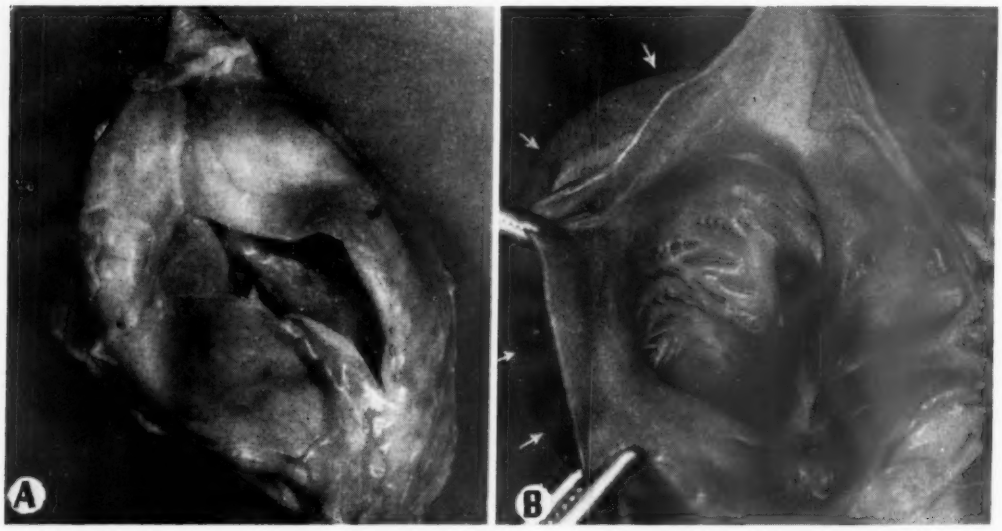

Fig. 2.—Photograph of a heart demonstrating a cyst which developed following placement of asbestos in the pericardium. *A*, Cyst opened. *B*, View from opened right atrium before opening cyst showing compression of atrioventricular ring. Arrows indicate borders of cyst in this view.

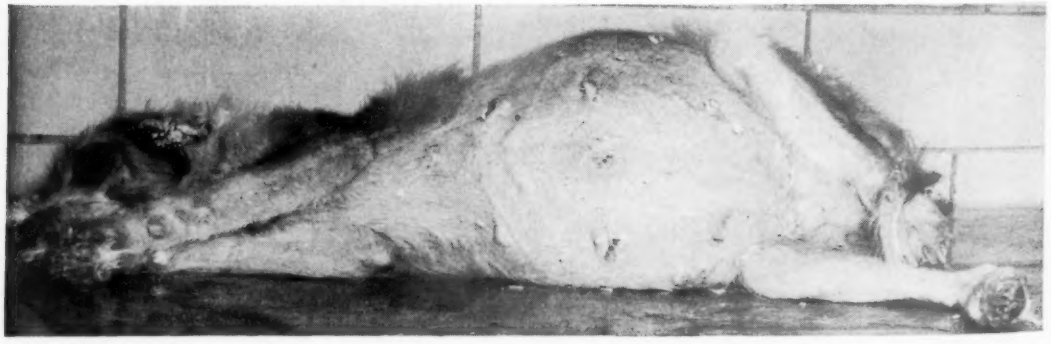

Fig. 3.—Photograph of dog with ascites as result of cyst compressing right heart.

On three occasions the abdomen of one (Fig. 3) was tapped, and 2,500 c.c. of ascitic fluid was removed each time. Venous pressure on one occasion was 96 mm. of water. On another occasion it was 210 mm. of water before paracentesis and 75 mm. of water afterward.

DISCUSSION

From this and other studies[9, 10, 14] there is convincing evidence that the mortality is much higher when coronary artery ligation has brought about occlusion of the septal artery. When the results of the present study are analyzed with this in mind, it is apparent that the use of asbestos affords the animal considerable protection, comparable to that resulting from ligation of the great cardiac vein. In animals with patent septal arteries, the mortality in untreated controls is 57.5 per cent, in those previously subjected to simple pericardiotomy* 27 per cent, in those with ligation of the great cardiac vein 12.5 per cent, and in those with intrapericardial asbestos 14 per cent. In animals with occlusion of the septal coronary artery as well as the anterior descending branch, the mortality in untreated controls is 100 per cent, in those with simple pericardiotomy 60 per cent, in those with ligation of the great cardiac vein 75 per cent, and in those with asbestos 61.5 per cent. Thus, in our hands the intrapericardial use of shredded asbestos affords the same order of protection as that given by great cardiac vein ligation. We have not studied the combination of these two methods. Beck and his associates[1, 2] feel that coronary sinus constriction, abrasion of the epicardium, and application of asbestos afford greater protection than the use of asbestos alone.

If one exceptional animal is excluded from consideration, retrograde coronary pressures, flows, and filling in injection studies are somewhat better in dogs studied 24 hours after ligation than in those studied immediately after ligation. As in animals with ligation of the great cardiac vein and in those with previous pericardiotomy, the retrograde coronary flows 24 hours after ligation are considerably greater than in the untreated group. The average retrograde coronary flow immediately after coronary ligation in the untreated controls and in animals with previous pericardiotomy, ligation of the great cardiac vein, or intrapericardial placement of asbestos ranged from 0.9 to 1.5 c.c. per minute. The flow averaged 1.0 c.c. per minute in untreated controls studied 24 hours after ligation. In contrast, flow studies made 24 hours after ligation in animals previously treated by pericardiotomy, vein ligation, or asbestos varied from 3 to 3.8 c.c. per minute. In the small number of asbestos-treated animals studied, there was not, however, clearly better retrograde filling on injection studies as had been found true in the groups with previous ligation of the great cardiac vein and simple pericardiotomy. The injection method which was used fills the distal arterial tree solely by virtue of intercoronary communications. These observations, then, might be interpreted as indicating that one month after the introduction of asbestos the protection afforded may be derived principally from new vascular channels between pericardium and heart. Obviously, more studies of this sort are needed. Furthermore, similar studies carried out at a later date might yield different results. Studies of this sort made one month after great cardiac vein ligation and simple pericardiotomy led us to believe that the benefit from these procedures was principally or entirely the result of better intercoronary communications.

*In a previous study[9] simple pericardiotomy was utilized as an operative control and was found to reduce markedly the mortality following coronary artery ligation. Studies indicated this beneficial effect resulted from improved intercoronary communications.

Schildt[7] and his colleagues called attention to the fact that there might possibly be some danger from the use of intrapericardial asbestos in large amounts since there might occur a collection of fluid between the two pericardial surfaces sufficient to cause cardiac compression. Though we used asbestos in the quantities recommended, such difficulties occurred in 25 per cent of the animals. It is of interest that the resultant cysts in all save one animal were located over the right atrioventricular groove and that all these animals developed ascites or pleural effusion and most of them died as a consequence. The importance of this specific location in the pericardial compression syndrome has been stressed by Parsons and Holman.[6] From our own work and that of Schildt and his associates it would appear that such complications could be avoided by using smaller amounts of asbestos, thoroughly abraiding epicardial and pericardial surfaces, and using care to distribute the material evenly over the surface of the heart. We know of no similar occurrence following the use of asbestos in patients.

From our small clinical experience with the use of epicardial abrasion and intrapericardial shredded asbestos, we are impressed with the fact that good results may be obtained by this method of treatment in cases of coronary artery disease with angina pectoris.

SUMMARY

A study of the use of intrapericardial shredded asbestos as a means of protecting the dog's heart from the results of subsequent coronary occlusion seemingly demonstrated clear benefit. The results compared favorably with those obtained from ligation of the great cardiac vein.

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CHEST CLINIC: "CLOSED CHEST INJURY"

JAMES H. FORSEE, COLONEL, MC, USA, HU A. BLAKE, MAJOR, MC, USA, AND E. M. GOYETTE, COLONEL, MC, USA, WASHINGTON, D. C.

(From the Surgical and Medical Services, Fitzsimons Army Hospital; the Departments of Medicine and Surgery, University of Colorado School of Medicine; the Medical Section, Army Forces, Far East, and the Military Advisory Group [Formosa])

UNSUSPECTED severe intrathoracic injury may follow minimal trauma to the chest wall. The mechanism is simple. A blunt force may so compress the thoracic cage that the deeper structures are damaged while the elastic recoil of the chest wall permits it to resume a normal configuration. Compensation claims add impetus for proper diagnosis and treatment.[20] Differential diagnosis is often difficult and seldom is the exact nature of the injury accurately evaluated at the initial observation. We have selected five groups of appropriate problems for presentation: pulmonary hematoma, traumatic lung cavitation, traumatic aortic aneurysm, obstruction of the great vessels, and cardiac contusion. The important "traumatic wet lung" classically described by Burford, Burbank, Brewer, and Samson[3, 4] is depicted in Fig. 1.

PULMONARY HEMATOMA

If as a consequence of chest wall trauma a large vessel or vessels within the lung are torn, the patient may complain only of expectorating blood-streaked sputum. Chest roentgenograms may reveal a discrete, rounded, solitary shadow similar to the indistinguishable "coin-like" lesions of granulomatous, hydatid, or neoplastic processes (Fig. 2).[6, 8, 12, 16] Difficulties are evident in establishing its benignity. In the absence of recent chest roentgenograms prior to the injury, the clinical history may be the only positive information suggesting the correct nature of the abnormal shadow. Surgical extirpation is indicated if the suspected hematoma does not regress in size in six to twelve weeks or if there is persistent cavitation. We have not encountered multiple pulmonary hematoma and the unnecessary removal of normal lung tissue is to be avoided. Three previous references to such pulmonary hematomas were found in the literature.[5, 17, 21] Four such cases have been under the observation of the authors.[16] It is probable that this is not an uncommon condition.

TRAUMATIC LUNG CAVITATION

If, instead of rupture of a large blood vessel, disruption of the lung parenchyma occurs, a traumatic pulmonary cavity or "cavity-appearing" lesion results. The experimental work of Moolten[14] probably explains this mechanism of cavity production. He was able to demonstrate that the creation of a parenchymal defect of any size or shape would result, on inflation of the lung, in a cavity of approximately circular shape which was larger than could be accounted for by the actual tissue destruction. Such behavior is attributable

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to the normal pulmonary elastic tissue pulling centrifugally in all directions. A zone of atelectatic pulmonary tissue is regularly observed surrounding the cavity.

Once one is aware of their occurrence, these cavities are usually readily recognizable.[13, 18] Their clinical behavior is in contrast to cavitation due to other causes. There is usually an absence of significant amounts of purulent sputum or systemic evidence of an infectious process. Rather rapid healing with minimal fibrosis is the usual course (Fig. 3). The importance of properly evaluating the chest wall injury and the roentgenographic shadow in traumatic

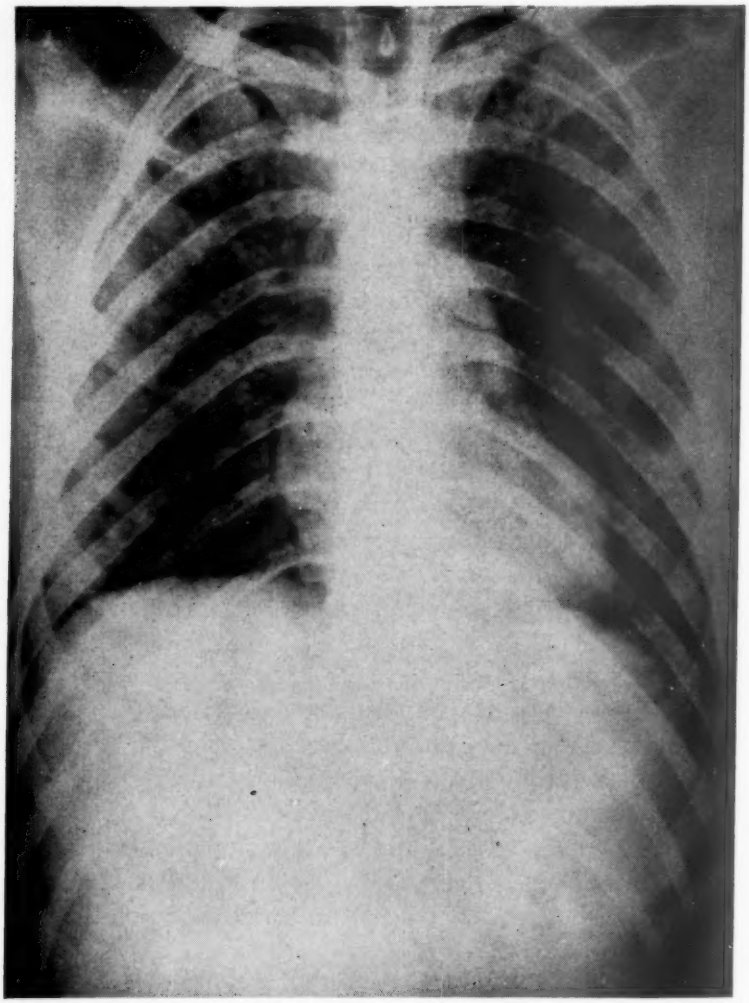


Fig. 1.—Traumatic wet lung. The chest wall was intact although there were automobile tire impressions on the skin of the anterior chest.

lung cavitation is twofold. First, to misinterpret this as a nonspecific lung abscess or of malignant etiology may subject the patient to unnecessary removal of normal tissue, and second, a prolonged period of hospitalization may result if the condition is erroneously considered tuberculous. Surgical extirpation has not been necessary in the patients we have observed. Surgical removal warrants consideration if the clinical course becomes complicated by suppuration or severe bleeding. Reference to traumatic lung cavitation is seldom found in the

literature.[2] We have not infrequently observed parenchymal cavitation in patients who have incurred penetrating or perforation wounds of the lung.

CASE 1.—A 23-year-old soldier had a negative chest roentgenogram when inducted into the Army in February, 1951. Eight months later he received minor lacerations to the chest wall when he was struck a glancing blow by the fender of a passing automobile. He fell to the pavement and incurred a head injury. A brief period of unconsciousness followed. The next day he complained of slight pain in the right chest. There was no hemoptysis. Chest roentgenogram revealed simple fractures of the right third and fourth ribs, posteriorly. There was a 5 cm. circumscribed, dense shadow in the right lower lung field (Fig. 2). During

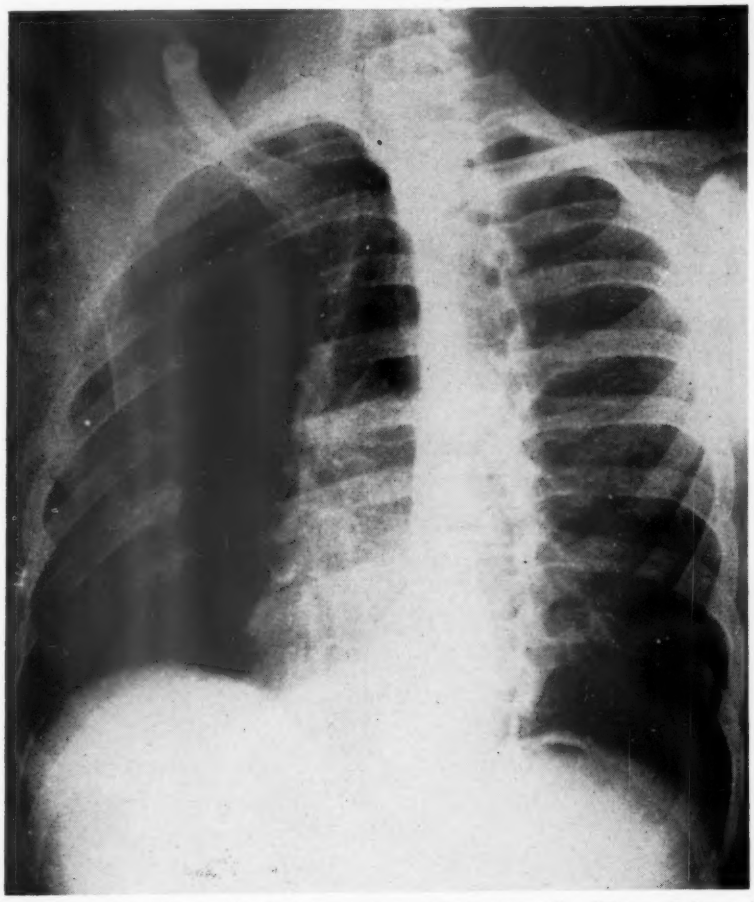
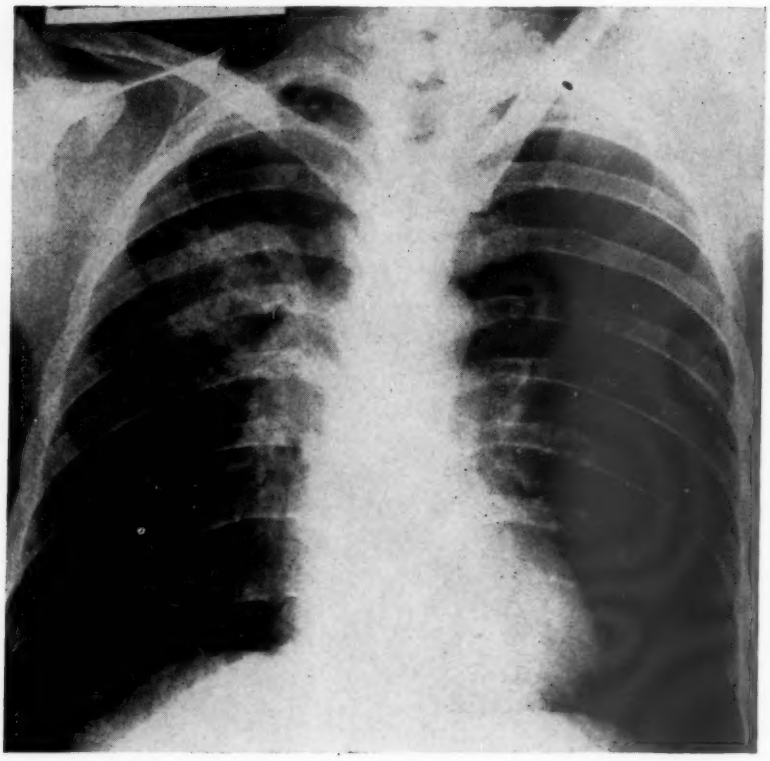


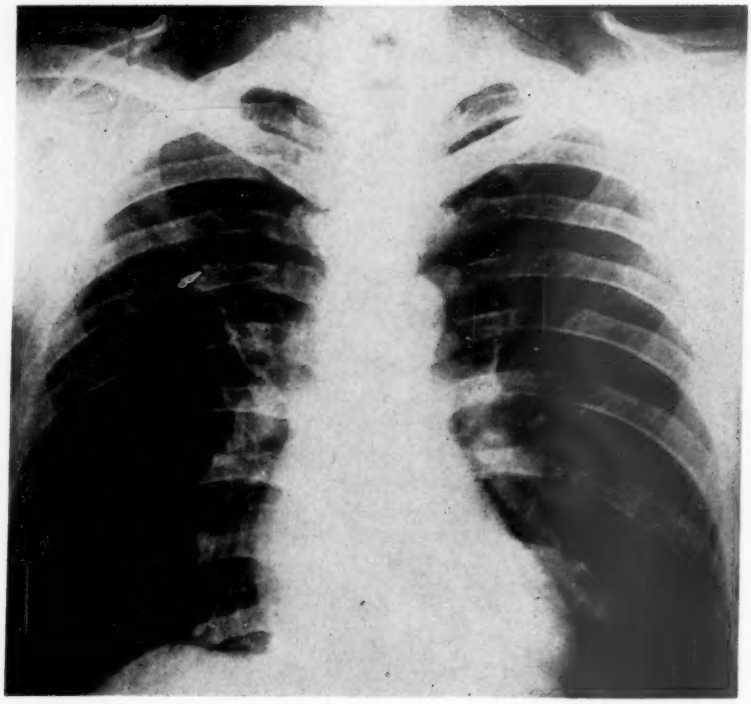
Fig. 2.—Oblique view of solitary discrete "pulmonary hematoma." (From Salyer, J. M., Blake, H. A. and Forsee, J. H., J. Thoracic Surg. 25: 336, 1953.)

the following eight weeks there was no apparent change in this shadow. The diagnosis was uncertain and we did not at that time appreciate the probability that this might be a pulmonary hematoma. Surgical exploration was advised and accepted. A five centimeter cystic lesion filled with blood, fading irregularly into surrounding compressed alveoli and fibrous tissue was removed by right lower lobectomy. Recovery was uneventful and the soldier returned to active military duty. He has remained well.

CASE 2.—This 30-year-old soldier incurred a superficial wound of the right upper anterior chest from a blunt tangential blow incurred at the time of an automobile accident. There was no suggestion of systemic injury. Chest roentgenograms did not indicate any osseous fracture. There was, however, evidence of a 6 cm. cavity within the right upper lobe, which in view of the clinical history of the chest wall injury was interpreted as a traumatic lung cavity. There was no recent x-ray examination of the chest, prior to injury, available. Rapid and complete healing occurred (Fig. 3, *A* and *B*).



A.



B.

Fig. 3.—*A*, Traumatic lung cavitation, right upper lung field, following closed chest injury. *B*, Same patient. Cavity has disappeared, leaving minimal fibrosis.

TRAUMATIC AORTIC ANEURYSM

A most fascinating problem has been that of the production of traumatic aortic aneurysm following chest wall injury. Within a period of eighteen months we observed three young soldiers who have survived trauma which compressed the chest wall and lacerated the aorta. In all instances, roentgenograms prior to closed chest injury were negative. All suffered clinical manifestations of shock, received whole blood transfusions, and were ambulatory in a few days. All other causes of aneurysm were investigated and found lacking. Initially a degree of healing takes place, yet ballooning of the weakened aortic wall with aneurysm formation gradually ensues. Ten etiologically similar cases have been described in recent literature.[1, 9, 11, 22]

CASE 3.—A 24-year-old soldier suffered from severe shock following an automobile accident in which the only external evidence of trauma was a superficial abrasion of the chest wall. Improvement was rapid and in a few days he returned to full military duty. Three months later, as a result of a routine chest roentgenogram made on the occasion of his re-enlistment, a large, unexplained shadow on the left was demonstrated. A review of the roentgenograms made immediately following the accident revealed definite widening of the mediastinum without aneurysmal formation. Angiocardiography demonstrated an 8 by 9 cm. aneurysm of the descending aorta (Fig. 4). Operative repair of the aneurysm was accomplished. Inspection of the interior of the aneurysm revealed a horizontal tear in the intima and media of the anterior aortic wall. The chest wall compression had, it was thought, resulted in a transverse tearing of more than half of the anterior circumference of the aorta, the tear being through the intima and media, but not the adventitia.* After a stormy postoperative period his convalescence was thought satisfactory until his sudden demise from hemorrhage seventy-one days after operation.

OBSTRUCTION OF THE GREAT VESSELS

We have observed one patient who incurred closed chest trauma who subsequently developed obstruction of the great vessels believed to be the result of the original injury. One other case report is recorded.[7] A 30-year-old soldier fighting in Korea was blown from his foxhole by bursting explosives. His only complaint was expectoration of blood-streaked sputum. He was observed at a clearing station for 72 hours and returned to his position on the front line. Nine months later abnormal findings were noted on chest roentgenographic examination and he was hospitalized at Fitzsimons Army Hospital for further study. Obstruction of the right pulmonary artery and superior vena cava was demonstrated by angiocardiography (Fig. 5). Definitive treatment was thought inadivsable in view of the location of the obstruction and the absence of clinical symptoms.

CARDIAC CONTUSION

Cardiac contusion as a result of closed chest injury is not infrequent.[17] Kissane[10] estimated that traumatic heart disease occurred in fifteen per cent of all chest injuries. In a study of 262 persons killed in accidents, Osborn[15] described traumatic lesions of the heart in nineteen. A rigid criteria as suggested by Sprague[19] should be followed if one is to avoid the mistake of attributing pre-existing heart disease to trauma. We have observed three different varieties of cardiac trauma following closed chest trauma. These have been subepicardial injury and arrhythmia, myocardial injury and congestive failure, and hemopericardium with resultant constrictive pericarditis.

*Dr. Henry Swan was the operating surgeon.

Fig. 5.

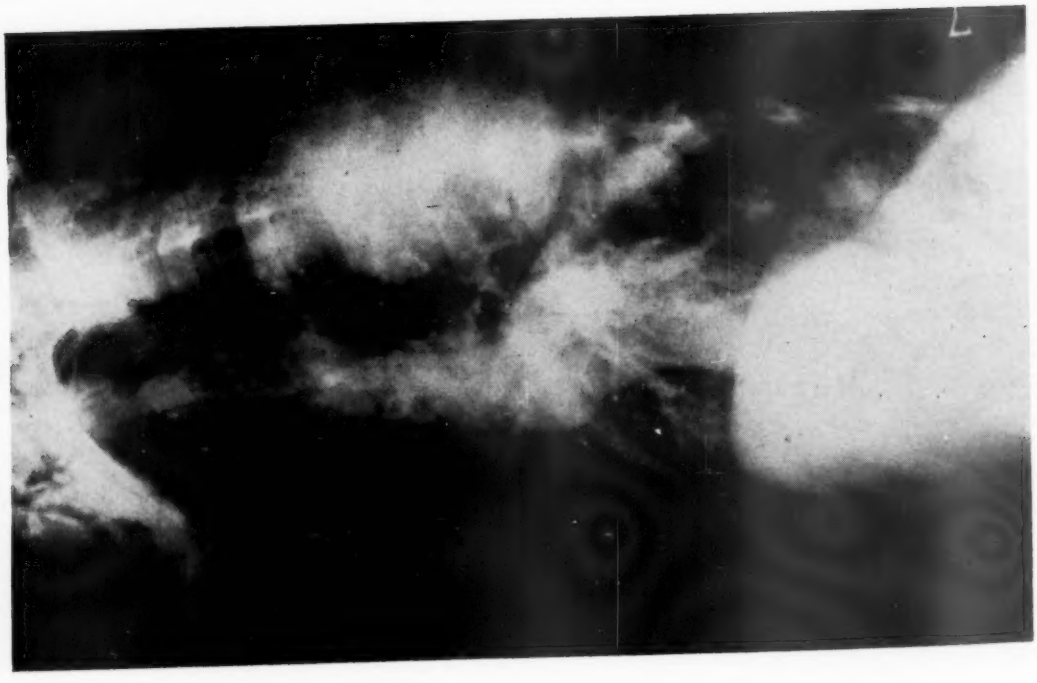


Fig. 4.

Fig. 4.—Aneurysm in descending aorta demonstrated by angiocardiogram following closed chest injury.
Fig. 5.—Venogram demonstrating block of superior vena cava following closed chest injury.

CASE 4.—This 30-year-old Army officer suffered what appeared to be a trivial chest wall injury as the result of an automobile accident. Nine hours later he had severe precordial pain associated with a friction rub. Serial electrocardiograms revealed ventricular tachycardia and widespread inversion of the T waves. Fluoroscopy demonstrated pericardial effusion. All abnormal findings gradually returned to normal, he became asymptomatic, and two and one-half months after the accident returned to full military duty.

SUMMARY

Emphasis upon the lack of appreciation that serious intrathoracic injury can occur in the absence of apparently significant injury to the chest wall itself, is strengthened by the scarcity of similar case reports. Pulmonary hematoma, traumatic lung cavitation, traumatic aortic aneurysm, obstruction of the great vessels, and cardiac contusion have been observed to follow what was considered minor trauma of the chest wall. The diagnosis is usually not considered at the initial observation. If considered, it is, however, usually not difficult. The treatment employed has been presented. The observation of patients who have incurred thoracic trauma should include chest roentgenography and at least a brief follow-up period after apparent initial recovery.

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Fig. 5.—Venogram demonstrating block of superior vena cava following closed chest injury.

SPONTANEOUS ATLANTOAXIAL SUBLUXATION ACCOMPANIED BY SEVERE NEUROLOGIC DEFICITS

ROBERT F. MABON, M.D., AND WOOD W. LOVELL, M.D.
ATLANTA, GA.

(From the Crippled Children's Division, Department of Public Health, State of Georgia)

INTRODUCTION

NOTHING is quite so startling as to see a child with wryneck lying in a distorted, twisted posture in acute distress, and obviously distrustful of any examination which will require manipulation of the head or neck. This report concerns two children having spontaneous atlantoaxial dislocation with neurologic deficits secondary to spinal cord compression. Although traumatic subluxation involving this level of the cervical spine is not uncommon, dislocation without obvious cause is relatively rare. Sullivan,[9] in a review of the literature, found 52 cases of this entity and reported 4 of his own. The average age of the reported patients has been thirteen years. Interestingly enough, spinal cord involvement has been reported in only rare instances and, apparently, only three cases of quadriplegia accompanying this lesion have been reported previously.[1, 10, 12]

ANATOMY

The atlas, or first cervical vertebra, supports the head and differs from all other vertebrae in that it has no body nor spinous process. It presents an anterior and posterior arch and a lateral mass on each side joining the arches. The lateral mass incorporates the superior and inferior articular processes. The superior processes are markedly concave for reception of the occipital condyles. On the posterior aspect of the anterior arch there is a small facet for the odontoid process of the axis. A small posterior tubercle represents a rudimentary spinous process. A transverse process projects from each lateral mass. The anterior portion of the central opening formed by the arches permits passage of the odontoid process, and the posterior portion contains the spinal cord. As previously mentioned, the superior facets of the atlas are deeply oval and concave, providing an insert for the occipital condyles. In contrast, the inferior facets are flat, oval, and inclined downward laterally and slightly forward. The axis, or second cervical vertebra, has a large spinous process, two small transverse processes, and the odontoid. The superior articular facets of the axis have the same characteristics of flatness and obliquity as described for the inferior articular facets of the atlas. This unique articulation is anatomically less stable than the junction between the base of the skull and the atlas (Fig. 1).

Flexion and extension movements of the skull are controlled primarily by the atlanto-occipital joint, whereas rotation occurs between the atlas and axis.

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These movements are permitted by the capsules of the articular processes, transverse ligament, and the alar ligaments. The transverse ligament stretches from one lateral mass of the atlas to the other behind the odontoid process, thus supporting the odontoid and separating it from the posterior compartment which contains the spinal cord. The alar ligament consists of a broad, thick band connecting the upper end of the odontoid process with the margins of the foramen magnum. These ligaments restrict extreme rotatory movements of the head. Grogone[5] found, in a fresh autopsy specimen, that when division of the transverse and accessory ligaments had been accomplished, considerable force was required to displace the atlas. He concluded that, in cases of spontaneous dislocation between the atlas and axis, there is necessarily relaxation of all the ligaments between these vertebral bodies.

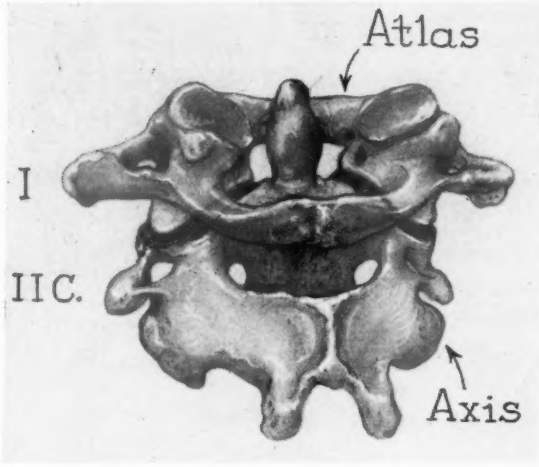

Fig. 1.

ETIOLOGY

Most authors agree with Bell,[2] who described the first case of this condition in 1830, that some sort of inflammatory process is the causative agent. However, there is a wide divergence of opinion as to the exact mechanism by which inflammation leads to displacement.

It is the opinion of Watson-Jones[11] that, in the presence of infection in the neck, there is an associated reactive hyperemia resulting in loosening of the ligamentous attachments, thus permitting subluxation. In one instance with displacement, he reported decalcification of the anterior arch of the atlas radiologically. Recalcification occurred following recovery from the infection. This idea is strongly supported by Greig[3] and the established experiments of Leriche and Policard.[7] The latter authors demonstrated decalcification of bone with increased blood supply, and its sclerosis with decreased blood flow. Other investigators, namely, Grisel,[4] and Hess and associates[6] have suggested that a combination of irritative spasm of the cervical musculature secondary to inflammation and the relaxation of the ligaments of this area may precipitate the subluxation.

SYMPTOMS AND SIGNS

In most cases this condition is preceded by, or is associated with, a severe cervical infection, usually in the nasopharynx. In addition to its being found with systemic diseases, such as rheumatoid arthritis and rheumatic fever, it is more frequently noted in pharyngitis, tonsillitis, influenza, retropharyngeal abscess, and cervical lymphadenitis. Minimal trauma, such as a quick movement during sleep or a slap on the back, can precipitate subluxation. However, in many instances, a careful history will elicit no evidence of injury. It is only fair to say that the latter probably represents true spontaneous subluxation of the atlas. The clinical features are quite striking.

1. In unilateral anterior displacement, one finds the occiput rotated toward the affected side and the head tilted anteriorly. The atlas may bulge into the posterior pharyngeal wall and be responsible for the nasal quality of the voice that is sometimes noted. The spinous process of the axis is palpable away from the affected side (Sudeck's[8] sign). All movements of the neck are restricted and painful. Neurologic examination is usually negative.

2. Bilateral anterior displacement may occur, in which case rotation is restricted to a greater degree. Compression of the spinal cord may result with positive neurologic findings. The head is tilted forward and the pharyngeal bulge is more prominent.

3. With unilateral posterior displacement, the occiput is rotated away from the affected side and the head extended. No pharyngeal bulge is present and the spinous process of the axis is rotated toward this side.

4. In the presence of an intact transverse ligament and odontoid process, posterior bilateral displacement is theoretically impossible.

DIAGNOSIS

Torticollis with restricted movements of the head and neck in a child who gives a history of associated cervical infection should make one think of atlantoaxial subluxation. Although radiologically it is difficult to visualize this portion of the cervical spine, in the majority of patients roentgenograms will confirm the clinical impression. The most revealing view is the open mouth position in the anteroposterior projection which will demonstrate the asymmetry or overlapping articular facets, narrowing of the joint spaces, and displacement of the odontoid process. However, because of the anterior displacement of the head, it is ordinarily difficult to obtain this view. In this situation, the routine lateral view will often demonstrate anterior displacement of the atlas. When the subluxation is minimal, anteroposterior stereoscopic views and laminography may be helpful. Anterior displacement of the atlas may be visualized in the lateral projection as a pharyngeal bulge angulating the nasopharyngeal air column.[1] In order not to overlook minimal neurologic deficits, the central and peripheral nervous systems should be examined carefully in all instances.

TREATMENT

Attempted reduction by manipulation under anesthesia is mentioned only to be condemned. Cervical traction is the accepted and ideal method of treatment of this lesion. Halter traction is usually unsatisfactory in this age

group but can be used occasionally in very mild displacement. Skeletal traction, by means of Crutchfield tongs, is much more satisfactory, particularly in severe displacement with evidence of spinal cord compression. The amount of weight used is governed by the degree of displacement, age and muscular development of the child, and the duration of time that the condition has existed prior to institution of therapy. Following clinical and x-ray evidence of correction of the displacement, one should use only enough weight to maintain the reduction. This is very important, in order to prevent overstretching and relaxation of the supporting ligaments and soft tissues. If this is not observed, when the traction is discontinued, redisplacement may occur. In uncomplicated cases, it is felt that traction should be utilized for a minimum of six to eight weeks. In patients with spinal cord involvement, a longer period of traction may be necessary. Immobilization should be employed after the traction has been discontinued for a period of several months. This can be in the form of an extension brace or plaster jacket. In cases of spinal cord involvement, which fail to respond to adequate traction and in which the neurologic findings persist or progress, decompression is mandatory. If this is done, fusion may be necessary in order to stabilize the atlas and axis. It is well to consider a trial of traction in the occasional desperate situation, with evidence of severe cord compression, because operative decompression may disastrously compromise medullary centers already in extreme jeopardy. If laminectomy is then necessary, it is suggested that local analgesia be employed whenever feasible. The use of endotracheal anesthesia, particularly in this condition, may cause further spinal cord damage due to the manipulation required to introduce an endotracheal tube. Decompression with the patient in traction might prove least hazardous. In the young child, where obviously general inhalation anesthesia is mandatory, a preliminary tracheotomy would be helpful in avoiding compromise of the spinal cord by the manipulations necessarily required to introduce an endotracheal tube.

CASE HISTORIES

CASE 1.—E. H. was an 11-year-old Negro girl seen for the Georgia Crippled Children's Division in Atlanta, Georgia, on Aug. 11, 1950. No relatives were available for information. Consequently, it was necessary to rely on the child's statements for a history, which proved inadequate. As far as could be ascertained, this child had been ill for a period of at least six months prior to being seen at the Clinic. This illness consisted of stiffness and pain in the neck with associated fever. About one month prior to the initial interview, she apparently lost the use of the right arm and leg. Her head had been drawn gradually toward the left shoulder and had remained that way since the beginning of her illness. Fever had been a constant feature, at times higher than others.

Examination revealed a child lying in a twisted, awkward posture with her head turned to the left and complaining bitterly of any attempt to manipulate the head even in a gentle fashion. There was a definite kyphosis of the upper cervical spine with a tender protuberance over the junction of the middle and upper portions of this area. The cranial nerves were essentially intact. The patient was unable to move any portion of either the right upper or lower extremity, presenting a picture of a total right hemiplegia. In the left upper extremity there was equivocal weakness of the interossei muscles as well as atrophy of the hypothenar musculature. Otherwise, motor power was well preserved throughout the left side of the body. The deep reflexes on the right were hyperactive as compared with a more physiologic response on the left. A sustained ankle clonus was encountered on the right but there was no evidence of a similar abnormal response of this

sort on the left. The cutaneous abdominal reflexes on the right could not be elicited, whereas they were briskly physiologic on the left. A strong extensor response to plantar stimulation on the right was evoked but, on the left, there was a plantar response to this maneuver. On testing sensation, touch was found to be well preserved throughout. However, there was definitely diminished sensation to pain and temperature over the entire left side of the body, whereas, elsewhere the sensory modalities were within normal limits, the total neurologic picture being consistent with a Brown-Sequard syndrome. Funduscopic examination revealed no abnormalities of either optic disc or retina.

Fig. 2.—Case 1. Lateral view of skull and upper cervical spine showing displacement of atlas anteriorly on the axis sufficient to reduce spinal canal more than 50 per cent.

Radiographs of the cervical spine were obtained. An attempt was made to secure an open mouth view of the odontoid but this was unsuccessful because of the fixed tilting of the head and neck. The lateral view disclosed approximately 50 per cent forward displacement of the atlas on the axis (Figs. 2 and 3). The patient was placed in skeletal traction using Crutchfield tongs and fifteen pounds of weight. With this treatment, the patient's head gradually rotated to a relatively normal position and, simultaneously, almost immediate improvement in the right hemiplegia, as well as return to normal of sensation throughout the body was noted. The patient was kept in traction until several days before the date of her discharge from the hospital, which was on Oct. 4, 1950. At that time, there was complete resolution of the hemiplegia and return of normal sensation as mentioned above. A moderate amount of wryneck was still evident, with the patient tending to tilt the head anteriorly and to the left. A neck brace was utilized for ambulatory and out-patient observation.

She did not return for follow-up examination until Feb. 2, 1955. At that time, she stated that she had no pain in her neck and that she had been attending school regularly. There was still a mild wryneck, the head being rotated slightly to the left side. No neurologic abnormalities were encountered. Flexion of the neck was found to be normal. Extension was limited to 50 per cent. Left lateral bending and rotation were also restricted approximately 50 per cent.

CASE 2.—J. P., a 13-year-old Negro boy, was seen initially at the Georgia State Crippled Children's Clinic in Atlanta, Georgia, on April 4, 1953. It was extremely difficult to obtain a reliable history but he was apparently in good health until May of 1952. At that time, he developed pain in the neck associated with headache. This neck discomfort was also accompanied by a high fever. A little later, after the onset of his illness, his neck and head were "pulled" to the right side. He was seen by two physicians who gave him some "shots." This did not help him. Later he developed progressive weakness in both the upper and lower extremities and within six months he was unable to walk. Voluntary control of the bladder was retained but he was unable to control bowel movements. The headaches persisted and were localized in the right temporal area.

Fig. 3.—Case 1. Anteroposterior view of cervical spine showing fixed position of head and and neck with chin rotated to right.

On examination, the child appeared as an acutely ill, Negro boy, looking his stated age, lying quietly in bed unable to turn or help himself in any fashion. He was completely unable to move his right upper extremity, his left upper extremity moved very weakly, and both lower extremities moved hardly at all. There was a level corresponding roughly to the third and fourth thoracic dermatome below which there was a complete loss to all forms of sensation. The deep reflexes were hyperactive but equal on both sides and there was an extensor response to plantar stimulation bilaterally. The occiput was turned to the right and the chin was tilted to the left side. There were only a few degrees of motion of the neck and these were found to be extremely painful. Roentgenograms revealed an anterior dislocation of the atlas on the axis (Figs. 4 and 5). He was admitted to the hospital and Crutchfield tongs were applied, using eighteen pounds of weight. Improvement was noticed immediately and his general condition became steadily better. Motor power returned to both the upper and lower extremities and the head and neck

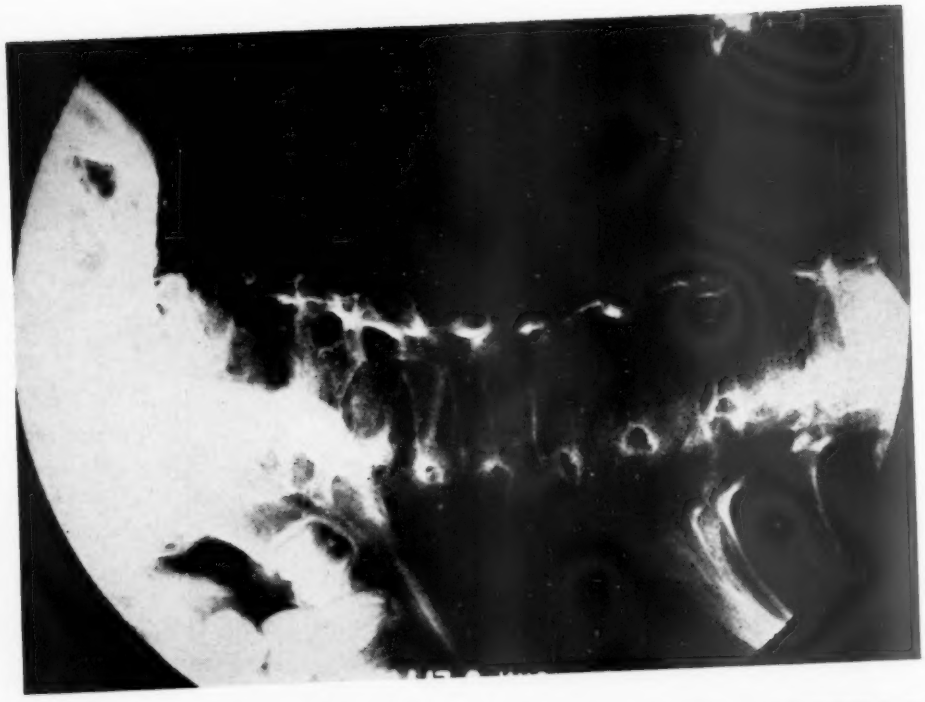

Fig. 5.

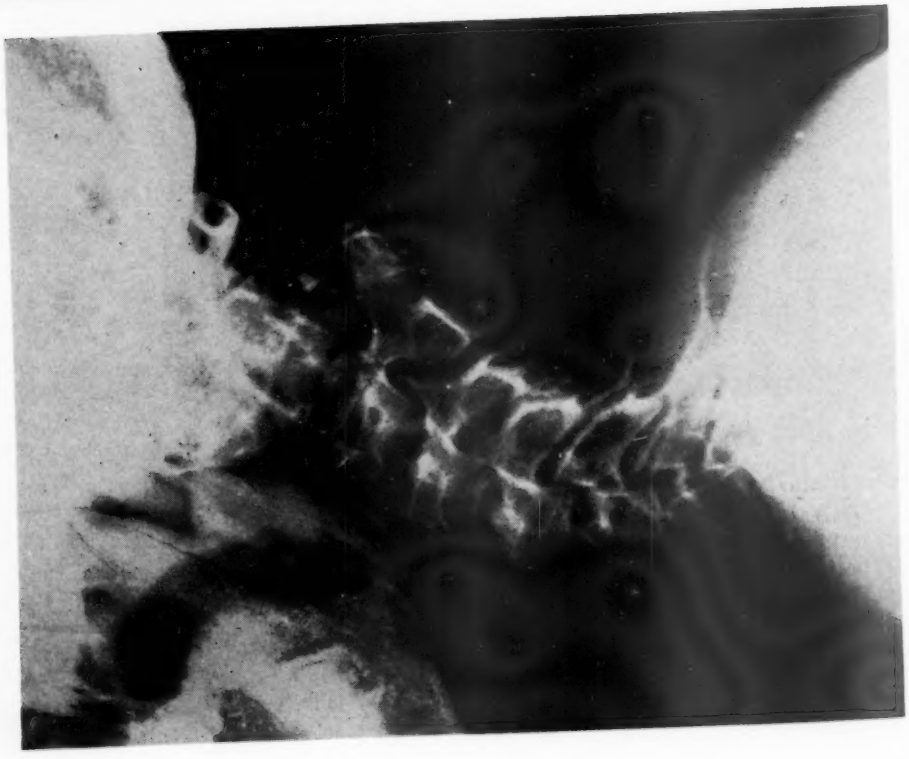

Fig. 4.

Fig. 4.—Case 2. Lateral view of cervical spine showing anterior dislocation of atlas on axis with reduction in spinal canal of at least 75 per cent.

Fig. 5.—Case 2. Frontal view of the cervical spine showing rotation of head and neck which is fixed.

could be turned to either side without difficulty. Voluntary control of the bowels also returned. Traction was discontinued after eight weeks and he was immobilized in an extension type of neck brace. He was discharged from the hospital walking in an almost normal manner. Shortly thereafter, he returned to school. The brace was discarded six months later. He was last seen Jan. 12, 1955, and at that time there was normal motor power in the upper and lower extremities. The neck pain had disappeared entirely and no further headaches had been noted. Flexion and extension of the neck was restricted 25 per cent. There was 30 per cent limitation of right and left rotation as well as lateral bending. The neurologic examination was entirely negative.

SUMMARY

Two cases of spontaneous atlantoaxial subluxation have been presented. The etiology of this condition is unknown but it is thought to be due to relaxation of the supporting ligaments. It is usually associated with acute upper respiratory infections or inflammatory diseases in and about the cervical area.

Associated spinal cord involvement has been reported only rarely and the two cases discussed in this report presented signs of hemiplegia and quadriparesis respectively.

The treatment of choice is traction. Mild cases may respond to halter traction alone but, with marked subluxation and, particularly, in those cases with cord involvement, skeletal traction, using Crutchfield tongs is the treatment of choice. Traction should be continued for a period of six to eight weeks in order to allow for healing of the ligaments and soft tissue. Immobilization should then be maintained, by means of a hyperextension brace or plaster jacket, for an additional four to six months.

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EFFECT OF EXPERIMENTAL BOWEL TRANSECTION ON SERUM AMYLASE LEVELS

JOHN H. SCHNEEWIND, M.D., CHICAGO, ILL.

(From the Department of Surgery, University of Illinois College of Medicine)

THIS investigation was undertaken to determine the effect of injury and perforation of the small intestine on serum amylase levels in dogs both in the fasting state and after feeding. As a method of creating a constant, efficient contamination of intestinal content we chose to transect the bowel. One of the stimuli to this study was our experience with a patient who suffered blunt trauma to the abdomen. A moderate elevation of the serum amylase helped in making a preoperative diagnosis of ruptured retroperitoneal portion of duodenum. This was confirmed at operation and the patient recovered. We assumed that the high amylase could have been caused by leaking of upper intestinal content into the peritoneal cavity or by trauma to the pancreas.

The point we wish to emphasize is that the serum amylase test may be extremely valuable as a diagnostic aid in conjunction with a careful clinical evaluation, but accurate interpretation of this test is a necessity. Furthermore, inaccurate interpretation of the test may result in serious errors in diagnosis.

In general, most of the papers dealing with clinical studies of acute abdominal disease and amylase levels agree on the following points. High amylase levels are usually an indication of acute pancreatitis; moderate increase of amylase levels may be due to duodenal or gastric ulcers with perforation or involvement of the pancreas, to small bowel obstruction usually with impairment of pancreatic drainage, to common duct stones, and to miscellaneous causes such as occlusion of salivary ducts and impaired renal function.

Probstein and associates[10] studied the blood amylase levels in 17 patients with perforated peptic ulcers. In four cases the serum amylase was moderately elevated; these ulcers "involved the pancreas."

Raffensberger[11] reported a series of 21 patients with moderate elevation of amylase levels due to causes other than primary pancreatitis. Included were 5 cases of perforated peptic ulcer, 4 of partial small bowel obstruction, 8 of acute peritonitis, and 3 of renal impairment with uremia.

Moretz and Erickson[7] compared the amylase levels of blood serum with those of peritoneal fluid obtained from 11 patients. Low levels were found in peritoneal fluids of patients with carcinomatosis, ascites, and small bowel

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obstruction without gangrene. Markedly elevated levels were found in patients with perforated peptic ulcer and pancreatitis, and the peritoneal fluid amylase levels were appreciably higher than the blood levels.

High amylase levels in peritoneal fluid in cases of acute pancreatitis have also been reported by Keith, Zollinger, and McCleery.[5]

The incidence of pancreatitis following abdominal surgery has also been investigated. Mahaffey and Howard[6] reported abnormal elevations of serum amylase in 27 out of 100 patients subjected to celiotomy. Patients with operations distant to the pancreas developed low amylase concentrations. Hotchkiss and associates[3] reported that of 23 patients who underwent operations in close proximity to the pancreas, 5 showed appreciable elevations of amylase levels, most of them occurring on the first postoperative day. The rest of the group of 47 patients had nonabdominal operations or operations distant from the pancreas and showed a consistent, moderate depression of amylase and lipase for the first six postoperative days. The implication of these latter two reports is that manipulation to or actual injury of the pancreas during operations in the upper abdomen occurs in approximately 20 per cent of cases.

In the preceding reports, however, the exact mechanism of the elevated blood serum amylase levels is really not evident. It is for this reason that our experiments were carried out.

Certain experimental studies previously reported are of interest. Waite[13] produced recurring pancreatitis in dogs by intermittent duct obstruction. His normal values in Somogyi units ranged from 900 to 1,500 with an average of 1,360. During attacks the values ranged from 2,000 to 6,600 with an average of 3,600.

Pemberton and associates[9] produced anterior perforations of the duodenum in dogs, which were closed with a soft rubber earplug. The perforation could then be reproduced at will. All of the 14 animals in their series were fed prior to perforation. Four, or 29 per cent, showed elevated serum amylase levels after perforation—the per cent rise ranging from 24 to 120 per cent. All expired. In the other ten animals with no rise of serum amylase there was a 50 per cent mortality rate.

These authors also injected pancreatic juice intraperitoneally in normal and depancreatectomized dogs and concluded that elevated serum amylase levels are dependent upon transperitoneal absorption in the presence of high amylase content of the peritoneal fluid.

METHOD

Twenty-six mongrel dogs of average size and in good health were used. Blood samples were taken prior to feeding at about the same time on an average of six successive days. The amylase values obtained were used as fasting controls.

Each dog was subjected to two operations. At the first operation a short piece of No. 25 gauge stainless steel wire was placed loosely around the duodenum 5 cm. from the pylorus. The peritoneum and fascia were closed around the wire, which was then covered by the subcutaneous tissues and skin. The animals tolerated this procedure well and

promptly resumed normal feeding. Following this operation, fasting blood samples were drawn on the first, second, third, sixth, and seventh postoperative days to serve as additional controls.

A week later a second operation was performed. This consisted of locating the wire through the previous skin incision and then transecting the duodenum by traction and a "sawing" motion with the wire. Blood samples were drawn at intervals of 1, 4, 24, and 48 hours. Daily samples were taken for three to seven days from those animals which survived. This operation was performed on 15 dogs in the fasting state and 11 who were fed approximately one hour prior to the operation.

The reason for staging the procedure rather than cutting the duodenum at the first operation was to eliminate the effect of direct operative trauma to the pancreas as much as possible.

The amylase was determined by a starch iodine method[12] which has been used in the hospital laboratories for approximately two years.

RESULTS

In Table I is shown the range and the average of the fasting control serum amylase levels in dogs. The range is 300 to 2,200 units per 100 ml.

TABLE I. SERUM AMYLASE LEVELS IN DOGS

	FASTING CONTROLS		AFTER FIRST OPERATION (PLACING WIRE AROUND DUODENUM) POSTOPERATIVE DAY				
			1	2	3	6	7
	RANGE	AVERAGE	AVERAGE VALUE				
Units per 100 ml. of serum	300-2,200	1,000	1,000	1,200	1,400	1,200	1,000

of serum and the average of these values is 1,000 units. It should be stated that this wide variation of 300 to 2,200 units did not occur in the same animal. We calculated the average of the daily fasting control and the per cent deviation from the average for each individual dog. The highest deviation was 86 per cent, the lowest deviation was 12 per cent. On this basis we concluded that any deviation of less than 100 per cent was not significant. The average values of the amylase on the first, second, third, sixth, and seventh days after the first operation are also shown. The small elevation which occurred returned to a normal range by the seventh day.

Table II shows the percentage of dogs which showed elevations of the serum amylase after the second operation, at which time the bowel was

TABLE II. PERCENTAGE OF DOGS WITH ELEVATED* SERUM AMYLASE AFTER BOWEL TRANSECTION

	HOURS AFTER TRANSECTION†			
	1	4	25	48
Fasting	7%	20%	60%	60%
Fed prior to operation	0%	0%	0%	0%

*At least 100 per cent above the average control figure.

†All 15 fasting dogs survived one and four hours after transection. Five dogs survived 24 and 48 hours. The percentages are based on the number of survivors with an elevated amylase.

transected. These readings were determined at 1, 4, 24, and 48 hours after transection. In the fasting group 7 per cent had a significant rise after one

hour, 20 per cent had an elevation after four hours, and 60 per cent after 24 and 48 hours, respectively. None of the animals fed approximately one hour prior to bowel transection had a significant elevation of serum amylase.

Table III reveals the amount of rise in amylase using the fasting controls as a base line. This includes only the animals which actually showed some

TABLE III. PER CENT ELEVATION IN SERUM AMYLASE AFTER EXPERIMENTAL BOWEL TRANSECTION

	HOURS AFTER TRANSECTION			
	1	4	24	48
Fasting	133%	177%	480%	520%
Fed prior to operation	18%	28%	10%	25%

elevation. We were rather surprised to note that the fasting animals showed appreciably higher rises than the animals fed prior to transection. In the fasting group at one hour the increase was 133 per cent, at four hours it was 177 per cent; by 24 hours the rise was 480 per cent over the control and at 48 hours it was 520 per cent. In contrast, the fed animals showed only 18 per cent rise at 1 hour, 28 per cent at 4 hours, 10 per cent at 24 hours, and 25 per cent at 48 hours. None of the elevations in the fed group was regarded as significant.

Table IV represents an analysis of survival in relation to rise in amylase levels. Only one-third of the fasting group survived. Of these 20 per cent

TABLE IV. RELATION OF SURVIVAL AND SERUM AMYLASE LEVELS FOLLOWING EXPERIMENTAL BOWEL TRANSECTION

	PER CENT SURVIVAL	PER CENT OF SURVIVORS WITH ELEVATED* SERUM AMYLASE			
		HOURS AFTER TRANSECTION			
		1	4	24	48
Fasting (15 dogs)	33	20	40	60	60
Fed prior to operation (11 dogs)	73	0	0	0	0

*At least 100 per cent above the average control figure.

Chi-square showed a p value of .05, indicating that the figures are statistically significant.

had elevated amylase levels one hour post transection, 40 per cent by 4 hours, and 60 per cent by 24 and 48 hours, respectively. In contrast, 73 per cent of the fed animals survived and none had a significant elevation of serum amylase.

Unusually high elevations of the serum amylase were found in two dogs, both in the fasting group. In one dog the 24-hour reading was 1,700 per cent over the control. The amylase levels returned to the control levels in five days. The animal was then eating well and appeared fully recovered. The dog was reoperated upon 14 days after bowel transection and the site of perforation was found sealed by omentum and surrounding structures. The pancreas was grossly normal. Another wire was placed and after a sub-

sequent transection the amylase rose to 1,000 per cent over the control values. At autopsy the pancreas was again normal in appearance without visible duct anomalies or obstruction.

DISCUSSION

The data in Table I reveals no significant rise in amylase, and presumably no pancreatitis due to placing the wire around the duodenum at the first operation.

The data in Table II reveals the percentage of fasting animals with a significant elevation of amylase (above 100 per cent) following transection of the bowel, as compared to the fed group in which there were no significant amylase elevations.

The extent of rise as shown in Table III came as a complete surprise. We had expected that feeding would stimulate pancreatic secretion and cause much higher levels. Instead, the fasting animals showed much higher values than the fed animals. One may speculate that the feedings acted to neutralize the pancreatic secretions.

Table IV illustrates that there is probably no relationship of animal survival to the level of the serum amylase. One-third of the fasting animals survived transection of the duodenum whereas 73 per cent of the fed animals survived. Sixty per cent of the fasting animals showed an elevation of the blood amylase at one of the four periods when blood specimens were drawn for analysis. This is in contrast to the fed animals, none of which had significant rises. Of the ten fasting dogs dying following transection of the duodenum only one showed an elevation of blood amylase over 100 per cent above the average of the preoperative control figure. These data along with that presented in Table IV suggest as intimated above that there is no relationship between the level of blood amylase following transection of the duodenum and the survival of the animal. The surviving animals were followed for an average of five days after bowel section. By this time they appeared healthy, were eating well, and their amylase levels were back to preoperative levels.

The obvious explanation is that feeding prior to operation in some way protected the dogs against the lethal intraperitoneal spillage of either pancreatic, gastric, or small bowel secretions. We must confess that this was a totally unforeseen finding and indicates the need for additional investigation into the lethal factor and a means to counteract it.

Unusually high amylase readings were obtained in two fasting animals after cutting the bowel. Should such a situation occur clinically—that is, perforation of the intestine with a high amylase—a diagnosis of acute pancreatitis might be made and conservative treatment, if instituted, might result in a fatality.

SUMMARY

The effect of acute bowel transection on serum amylase levels was investigated in a series of 26 dogs. These were divided into two groups—one

fasting and one fed just before transection. Control amylase readings were taken on all animals prior to operation and ranged from 300 to 2,200 with an average of 1,000 amylase units per 100 ml. of serum.

The possibility of production of pancreatitis by operative trauma was nullified by placing a stainless steel wire around the duodenum at a preliminary operation. The slight elevation of amylase values returned to the control level by the time the bowel transection was performed at a second operation a week later.

After bowel transection as many as 60 per cent of the fasting dogs showed elevated amylase readings at one of the four periods when blood was taken for analysis. None of the dogs in the fed group showed a significant elevation (i.e., at least 100 per cent above the average of their control figures). The actual amylase elevation was strikingly higher in the fasting than in the fed animals. The figures are shown in Table III. Also of interest is the fact that while one-third of the fasting animals survived bowel transection, 73 per cent of the fed animals survived; this might suggest that there is a protective action of food against the lethal effect of intraperitoneal spillage of gastric, pancreatic or intestinal secretions.

In three cases, unusually high amylase readings were obtained after bowel transection in fasting animals. Should a high reading of this type be encountered clinically in patient with bowel perforation, a diagnosis of acute pancreatitis might be made and if treated conservatively (as is customary for acute pancreatitis) a fatality might result.

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THE USE OF AN ANTIHISTAMINE AGENT IN PREVENTING SERUM REACTIONS FOLLOWING THE INJECTION OF TETANUS ANTITOXIN

A. O. Singleton, Jr., M.D., and Harry M. Little, Jr., B.A., Galveston, Tex.

(From the Department of Surgery, Medical Branch, University of Texas)

ALTHOUGH the increase in immunization of individuals against tetanus with tetanus toxoid in recent years has reduced the necessity of giving prophylactic tetanus antitoxin injections, serum reactions from tetanus antitoxin continues to remain a major problem. More of our University of Texas Medical Branch employees have been hospitalized for antitoxin reactions than for actual injuries.

Serum sickness is a systemic reaction occurring usually within two weeks following the introduction of a foreign serum, and it usually runs a course of about two days. It is now agreed among most observers that the manifestations occurring in this disease are due to the interaction between antigens contained in the injected serum and specific antibodies produced by the recipient in response to the antigenic stimulation. The manifestations of serum sickness in a full blown case are most commonly skin eruptions (urticaria, purpura, or erythematous eruptions), pruritis, fever lymphadenopathy, abdominal pain, nausea and vomiting, polyarthritis, and often edema of the eyelids, face, and ankles. In patients already sensitized from a previous injection of serum, or by the less common oral, bronchial, or placental methods of sensitization, these manifestations may develop in a shorter length of time than in nonsensitized patients. Though it is not too common, serum injected into hypersensitized patients can cause immediate and severe reactions, with death often rapidly following.[3, 6, 10]

In the case of tetanus antitoxin prophylaxis, it may be expected that about 10 per cent of the patients receiving the normal course of 1,500 International Units will develop serum sickness reactions of varying severity some time within the following two weeks, even with the present day use of highly purified protein digested serum.[1]

Serum sickness reactions can usually be controlled with epinephrine, antihistamines, sedatives, and finally cortisone and ACTH in severe cases. However, a suitable prophylactic agent to prevent the occurrence of serum reactions has yet to be developed. In 1906, Netter[9] reported that calcium was helpful in reducing the incidence of these reactions, but it was not of much benefit in the hands of other investigators. In 1922, Kraus[7] reported a very low incidence of serum sickness reactions by using bovine serum instead of horse serum. Levy,[8] in 1933, reported the use of ephedrine to lower the

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incidence of serum sickness reactions, but its use has since been disputed. Foshay and Hagebusch,[4] in 1939, and later Cherry and Prickman,[2] in 1941, claimed favorable results in the prevention of serum sickness by using the enzyme, histaminase. More recently, Waxman and Geshelin,[11] in 1951, reported in a series of 100 cases in whom, when 50 mg. of oral Pyribenzamine was given each day for ten days following the prophylactic injection of 5,000 u. of tetanus antitoxin, the incidence of serum sickness reactions was 3.6 per cent, whereas the incidence of serum sickness reactions occurring in patients not given Pyribenzamine was 20.4 per cent. This would seem to be a relatively small series of cases from which to draw conclusions. We were amazed to find so little material in the literature on this subject despite the common interest and the importance of this problem.

In 1953, we were asked by the manufacturer to try the antihistamine, Phenergan, in the emergency room of the John Sealy Hospital in order to evaluate its usefulness in preventing serum reactions following tetanus antitoxin therapy. Phenergan is the N-dimethylaminopropyl derivative of phenothiazine, and its antihistaminic properties were discovered in France in 1946.[5] The manufacturers of Phenergan supplied the information that several investigators had reported to them by letter that in a large series of cases the use of Phenergan had reduced the occurrence of serum sickness reactions from tetanus antitoxin to less than 1 per cent and those reactions that did occur were mild. The results of these investigators remain unpublished to our knowledge.

In order to determine the effectiveness of oral Phenergan in the prevention of serum sickness reactions due to tetanus antitoxin, a control group of 250 patients receiving tetanus antitoxin alone was compared with a group of 250 patients receiving tetanus antitoxin and Phenergan.* Starting in December, 1953, the records of 500 patients subsequently receiving tetanus antitoxin prophylaxis in the emergency room of John Sealy Hospital were reviewed to determine the incidence of serum sickness reactions. The first 250 patients received tetanus antitoxin alone and after records on these cases were reviewed, the next 250 patients receiving tetanus antitoxin were also given Phenergan prophylaxis. The course of Phenergan prophylaxis used was as recommended by its manufacturer: 12.5 mg. at the time of injection of tetanus antitoxin, 12.5 mg. the following night, and 25 mg. each night thereafter for seven days.

Transients and other patients who did not return to the hospital for a checkup for their primary condition were not counted in the two 250-patient groups. Thus, the data collected do not consist of 250 consecutive patients in each group.

All patients were skin tested prior to tetanus antitoxin injection and those patients showing a positive reaction were given their course of tetanus antitoxin in divided desensitizing doses.

The incidence of serum sickness reactions in the two groups is shown in Table I. The incidence of reaction was 11.2 per cent where tetanus antitoxin alone was given. This dropped to 7.2 per cent in the group where Phenergan

*Supplied through the courtesy of Wyeth Laboratories.

TABLE I. INCIDENCE OF SERUM SICKNESS REACTIONS OCCURRING IN 250 PATIENTS RECEIVING TETANUS ANTITOXIN PROPHYLAXIS VS THOSE OCCURRING IN 250 PATIENTS RECEIVING TETANUS ANTITOXIN PROPHYLAXIS AND PHENERGAN

	NUMBER OF PATIENTS	NO REACTIONS	REACTIONS	PER CENT REACTIONS
Tetanus Antitoxin alone	250	222	28	11.2
Tetanus Antitoxin and Phenergan	250	232	18	7.2

was given also. The type of serum sickness reactions occurring ranged from very mild skin manifestations to fairly severe generalized reactions; however, it could not be said that the reactions occurring in one group of patients were milder or more severe than reactions occurring in the other group of patients.

Using the exact method of Chi Square in analyzing the results statistically, Chi Square is 2.847 and P is slightly less than 0.10. This means that one could expect the same results as obtained to occur about 10 times out of every 100 just by chance alone. Therefore, the decrease in incidence of serum sickness reaction by using prophylactic Phenergan does not appear to have much statistical significance.

SUMMARY

Antihistamines have been recommended in preventing serum reactions from tetanus antitoxins although there is little information in the literature to substantiate this. In comparing 250 patients who received tetanus antitoxin alone with 250 patients who received tetanus antitoxin and Phenergan we found no conclusive evidence that this substance lessened the incidence of serum reactions.

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Editorial

The National Library of Medicine

THE medical profession in the United States can be justly proud of the Armed Forces Medical Library, which has the largest collection of medical literature in the world and which, without a doubt, is the finest medical library in existence. Unfortunately, however, the Library, which was established in 1836, has completely outgrown the quarters in which it has been housed since 1887. In fact, since 1942, because of lack of space in the Washington area, a portion of the Library has been housed in leased quarters in Cleveland.

Appreciating the need for adequate facilities for this splendid Library, the Task Force on Medical Services of the Hoover Commission recommended that a new building be constructed. The original recommendation was that it be placed, for organizational purposes, under the Smithsonian Institute. However, since there is little relationship between the Smithsonian Institute and the Armed Forces Medical Library, it has been suggested by Senators Lister Hill and John Kennedy that the Library be established as an independent entity, and these gentlemen have introduced into the Senate of the United States a bill (S-3430) "To promote the progress of medicine and to advance the national health and welfare by creating a National Library of Medicine." Although this bill calls for the establishment of the National Library of Medicine as a separate entity, it has been subsequently suggested and recommended by the Armed Forces Medical Library Advisory Group that, instead of establishment as an independent institution, the Library should be placed under the jurisdiction of the Public Health Service. Considerable saving in administrative cost would thereby be accomplished and a much more efficient operation would be possible. This seems an admirable recommendation.

Because this unique library is so essential to progress in medicine, and because most of the other medical and scientific libraries in the United States and even the rest of the world are dependent upon it for reference, any legislation which will establish a permanent housing facility for the Library should have the hardy support of all the medical profession.

—*Alton Ochsner.*

Note: Since the above was written, the Bill (S-3430) has been passed and has been signed by President Eisenhower. The Bill authorizes that the National Library of Medicine will be under the direction of the United States Public Health Service and that there will be a Board of Regents of twenty members who will be appointed by the President.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

THE PATHOLOGY OF THERMAL BURNS—CHANGING CONCEPTS

A REVIEW OF THE LITERATURE SINCE 1945

JOHN H. DAVIS, M.D.,* AND WILLIAM E. ABBOTT, M.D., CLEVELAND, OHIO

(From the Department of Surgery, Western Reserve University, School of Medicine and the University Hospitals of Cleveland)

INTRODUCTION

THE fact that we are living in an era of increased susceptibility to a major disaster, either civilian or military, makes it imperative that all physicians stay abreast of the changing concepts of the pathology of burns.

The Metropolitan Life Insurance Company figures[90] indicate that 4,600 persons die annually in the United States from burns and scalds. The incidence of nonfatal burns can only be estimated, but it is sufficient to create a constant problem for the physician in both industry and the home.

Previous reviews have covered the subject up to 1946.[31, 42, 56, 71] The purpose of this paper is to present some of the more recent advances that have been made in the study of the pathophysiology of thermal injuries.

SKIN

The threat of atomic warfare has increased the need for precise knowledge regarding the thermal tolerances of living tissue, particularly the skin, and the nature of the cellular and somatic changes that are induced by hyperthermia. Henriques and Moritz,[49] using the pig as an experimental subject, investigated the various physical factors which affect the transfer of heat to and through the skin, and developed a general theory of heat flow by which the time-temperature relationships within the skin during exposure to heat could be estimated. The inward flow of heat depends upon (1) the ability of the skin to absorb heat, and (2) its ability to conduct it. Measurement of the interface temperature at the junction of the dermis and fat by means of a needle thermocouple revealed the rapid development of edema of the corium at surface temperatures ranging between 50° and 70° C. When skin surface temperatures were raised above 80° C., edema developed more slowly and at a deeper level. With constant heat application up to 70° C., the accumulation of fluid tended to absorb heat and to protect the deeper tissues. Measurement of

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*U.S. Public Health Service Post Doctorate Research Fellow.

the effect of heat on the basal cell layer of the epidermis was then carried out under two different experimental conditions, (1) when the source of heat was at some distance from the epidermis and the heat was transferred through the air, and (2) when the surface temperature was immediately brought to and maintained at the source temperature. The latter showed at least a thousand times greater ability to injure the epidermis than a heat source which raises the skin temperature by means of irradiation. Moritz and Henriques[64] have also shown that it is necessary to know both the intensity and duration of the exposure to heat in order to compute its capacity to destroy the epidermis. Skin temperature maintained at 44° C. required approximately six hours before irreversible damage was done to the basal cell layer. If the temperature was increased to 70° C. and higher, the rate of injury was so rapid that less than one second was required to cause transepidermal necrosis. In the third paper of this series[65] the cytological and histological manifestations of hyperthermic cutaneous injury were reported. The earliest change is a redistribution of chromatin within the nuclei, first in the intermediate and later in the deep cell layers of the epidermis. If the injury is deeper, swelling and disintegration of the cytoplasm of the basal cells and of nuclei throughout the entire thickness of the epidermis occurs. Because of these changes in the basal cells or in the intercellular cement that binds them to the dermis, an irreversible impairment of the attachment between the epidermis and dermis occurs. This correlates very well clinically with the layer of epithelium that frequently can be very easily peeled off the burned surface. A further rise in the temperature causes the following changes in the epidermis in succession: coagulation, progressive desiccation, and finally carbonization.

Changes in the dermis undergo a similar course based again on the temperature and duration of exposure. The earliest change in the dermis is an immediate constriction of the small vessels (arterioles) followed by vasodilatation. There occurs at this time an increased permeability of the capillary membrane and edema formation. The formation of the edema promotes the vesiculation which is seen as the epidermis separates from the dermis. As the temperature continues to rise in the dermal layer, coagulative changes occur, and further temperature rise results in desiccation and finally carbonization. These changes are diagrammatically represented in Fig. 1.

Entin and Baxter[30] produced a standard burn in human beings under anesthesia, utilizing an apparatus of their own design. The instrument was able to deliver directly to the skin through a metal plate a constant caloric output, and the effects of temperatures up to 110° C. were studied. The pathologic findings were very similar to those described by Moritz and coworkers, but the former authors concluded that human skin was able to withstand any particular temperature range for a slightly longer period of time than pig skin before irreversible injury occurred. They stress the difficulty in correlating the depth of a burn with its surface appearance and believe that biopsies taken early and again at 48 and 72 hours will enable the clinician to estimate the depth of burn more accurately.

Sevitt[85] studied the circulation of the small vessels beneath the burned area. Using the double-dye technique he recognized two kinds of full thick-

ness burns, (1) those due to direct heat necrosis of the dermis, and (2) those due to stasis of the blood flow. Direct observation with a microscope of the small vessels in the burned area revealed that the flow through these vessels became stagnant, the red cells adhered in clumps (sludging), and, finally, that the tightly packed masses of red cells blocked the capillaries and veins.

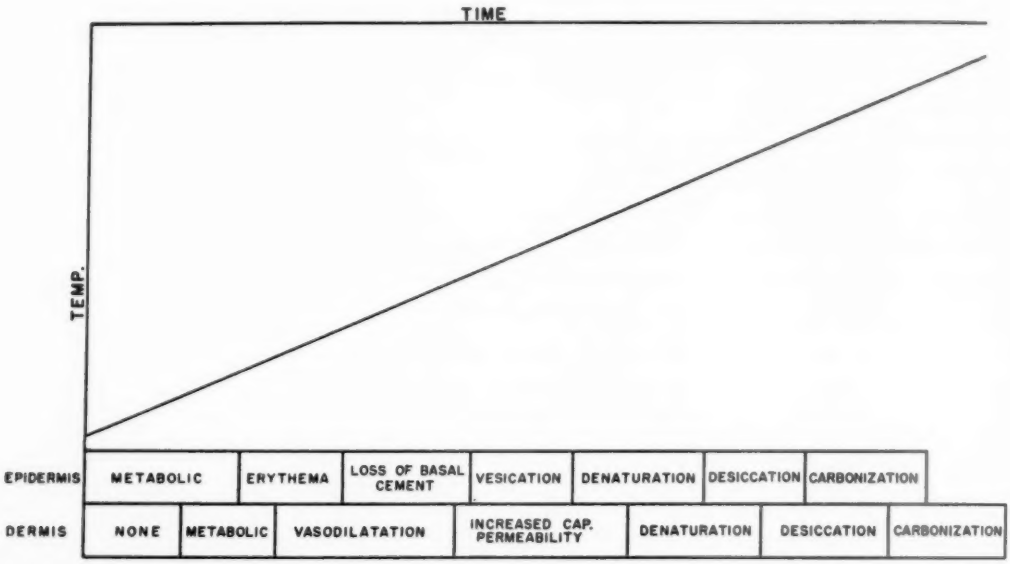

Fig. 1.—Effect of increasing time or temperature of directly conducted heat on the histopathology of skin.

Whether or not these clumped red cells are actual thrombi in the veins is unknown. At any rate, stagnant anoxia occurs and a complete slough of the overlying skin takes place. A number of cases were seen by Sevitt in which stagnation of the blood flow was observed, and yet full-thickness skin loss did not occur, and he concluded that either cessation of the blood flow did not follow the stagnation, or that it was localized to the superficial part of the dermis. Brooks, Dragstedt, Warner and Knisely,[8] utilizing the transillumination technique of Hoerr,[52] studied this same problem. They noted the intravascular agglutination of red blood cells into distinctly visible, smooth, hard, rigid masses. These resisted passage through the small vessels, arterioles, capillaries, and venules. In addition, white blood cells were noted to stick to the vessel's wall and laminar blood flow ceased. They concluded that the most definite and easily observed change was the decreased rate of flow following the burn. Further observations revealed red blood cells present extravascularly without direct evidence of rupture of the vessels, and also red cells seen in the phagocytes of spleen, liver, and bone marrow of recently burned animals. These authors present the hypothesis that the sludging of the blood, which occurs following the burn, may be one of the important factors in the cause of burn shock. It would be of great interest to know if sludged red cells are functionally inactive and therefore lost to the circulation.

In order to prevent further tissue damage by delayed clotting of the blood circulating through the small vessels of the burned skin, Parsons, Alrich, and

Lehman[72] evaluated the effects of heparinization. Standard burns were carried out in rabbits by immersing their ears in hot water at 65° C. for five seconds. The smallest average tissue loss (almost 40 per cent of the burned area) was seen in heparinized animals whose ears were allowed to be dependent. The control group had a tissue loss of 52 per cent of the burned area, the group that was not given heparin but the ears kept elevated had a 63 per cent loss, and the animals which were heparinized and the ears elevated had a loss of 65 per cent of the burned area. They used fluorescein dye injection and ultraviolet light to determine the underlying circulation in the burned area at varied intervals of time. These authors concluded that there was a delay of at least four hours after burning before vascular occlusion occurred unless the intensity of the initial heat was great enough to cause immediate coagulation. Heparin seemed to delay the onset of clotting and to diminish the amount of tissue loss. Elevation appeared to overbalance the effects of heparinization and dry gangrene occurred earlier and tissue loss was greater. Elrod, McCleery, and Ball[27] have also studied this problem experimentally. Thirty-six animals were burned by immersion in hot water at 100° C. for ten seconds over an area ranging between 39 and 52 per cent of the body surface. Sixteen animals served as controls, 10 animals were heparinized immediately before the burn, and 10 animals were heparinized two hours after the burn. No parenteral therapy was given, and survival time was evaluated. Statistical analysis of survival time in this study revealed that the increased survival would occur by chance less than one in a thousand times (p value of less than 0.001). They also demonstrated a significantly smaller rise in nonprotein nitrogen in the treated animals, and an apparent decrease in the expected hemoconcentration and believed that the latter was due to the preventing of blocking of the lymphatics and thereby a better return of fluid and albumin to the circulation. They also suggested that heparin may have some effect in altering a protein toxin if one exists. Alrich[2] studied the effect of heparin on blood plasma and proteins in experimental burns. Dogs were burned by immersion in hot water at 75° C., having first been anesthetized with Nembutal. The animals were anesthetized for the entire period, the maximum survival time being 30 hours. There was a greater loss of plasma volume during the first 12 hours after burning in the heparinized as compared with the nonheparinized animals. This was shown by the decrease in plasma volume (T-1824), a drop in total plasma proteins, and a rise in the hematocrit. However, from 12 to 30 hours after burning, the opposite effects were noted. There was an increase in plasma volume and total proteins and a greater fall in the hematocrit value in the heparinized series. Alrich believed that the effect of heparin was in the prevention of coagulation of the exudate in the tissues and the lymphatics, thus initially resulting in a greater loss of fluid but subsequently permitting a greater return of the fluid via the lymphatics to the circulation. The mortality was greater in the heparinized group. Two of the five animals died of gross hemorrhage. He concluded that heparin should not be used clinically because of the increased mortality rate. These studies seem

to indicate that anticoagulants might possibly be of some value in burn therapy, but further clarification as to their beneficial or harmful effect is needed before they can be advocated for clinical use.

Campbell, Gabriel, and Van Hoek[10] made a detailed study of the clotting mechanism in thermal injury. Thrombocytopenia of a rather marked degree (62 per cent below the normal mean) occurred in most cases, reached a maximum by the seventh day, and then gradually returned toward normal. The prothrombin time was seen to fall markedly in those patients who died in the first twenty-four hours, while, in those who survived, the prothrombin time rose to approximately 11 per cent above normal, gradually returned toward normal, and then began to fall from approximately the thirtieth day on, falling to about 50 per cent of normal. A few patients showed an increase in accelerator globulin twenty-four hours after burning. All showed an extreme rise in fibrinogen to as high as 130 per cent of the control level, starting at the time of burning. Prendergast, Fenichel, and Daly[74] studied the serum proteins in burned patients by means of electrophoresis and found the following changes: there was a decrease in albumin in all cases, which started at the time of injury and progressed to a low point several days post burn. The albumin titer began to rise as recovery occurred. The gamma globulin fraction seemed to be the best indicator of the severity of the burn. In all cases there was a rise in the gamma globulin factor and this seemed to correlate with the severity of the burn. It reached the highest level in the patient who died. These authors also found a rise in the fibrinogen titer. They suggest that since the liver is the site of formation of albumin and fibrinogen it is stimulated to increase production by the albumin lost through the burn wound. Because the liver is producing albumin, it also produces fibrinogen; hence the characteristic finding of a rising fibrinogen level while the liver is attempting to compensate for a falling albumin level.

Campbell, Gabriel, and Van Hoek[10] also demonstrated that the blood viscosity increases in the early phase of the burn (period of shock) probably due to the loss of plasma through the injured capillaries, but usually returns to normal by the fourth day. Quinby and Cope[76] also studied the problem of viscosity in burned dogs and patients, and showed that the viscosity paralleled the changes in the hematocrit and serum protein concentration. Both groups of workers were unable to show any harmful effects of the increased viscosity, but suggest that it is probably better therapeutically to attempt to keep the viscosity as near normal as possible. Abbott and associates,[1] in discussing the use of whole blood in the treatment of burns, also noted the hemoconcentration when inadequate amounts of an electrolyte solution were administered. They emphasized that changes in the blood viscosity were dependent upon a rise in the fibrinogen and globulin fractions, as well as a rise in the concentration of red cells. Since hemoconcentration can be avoided if adequate quantities of an electrolyte solution are employed and excessive rises in the fibrinogen and globulin titer might result from the administration of plasma, they preferred the use of whole blood and an electrolyte solution in the treatment of burn shock.

Campbell, Gabriel and Van Hoek[10] carried out protamine titration tests and failed to show any evidence of heparin or heparin-like substances being released into the blood stream in excessive quantities. They noted that mild to severe hemolysis was common in the first few hours after burning; it was seen to clear rapidly in the surviving animals, but remained for 24 to 48 hours in the animals that succumbed.

Although marked changes in some of the elements of the clotting mechanism were seen in these experiments, there was no evidence that any defect in the coagulation mechanism resulted from these changes. These studies also indicate that there is no reason to believe that thrombosis would be any less in this group than in any other group of seriously injured patients.

TOXINS

A number of burned patients die without demonstrable gross or microscopic evidence adequate to explain the cause of death. Because of this, there has been a continual search for the lethal toxin or toxins which are released from the burned area into the blood stream. As our knowledge of the fundamental chemical changes that occur in burned tissues increases, the cause of death in many burned patients can be more easily explained. Although the existence of a toxin has not been completely ruled out, none has been found to this date, and a careful study of the clinical and laboratory data usually reveals the cause of death.

Roos, Weisiger, and Moritz[77] studied the problem of instantaneous death from severe burns and proposed two possible mechanisms: (1) heat of great intensity can actually raise the temperature of the blood stream high enough to produce a direct thermal effect on the heart and brain, causing death. (2) extensive burns cause a release of potassium from the burned tissues into the blood stream. The source of most of this potassium is from the erythrocytes of the circulation and, therefore, depends on a heat of sufficient intensity to actually destroy a large number of circulating red cells. When massive red cell destruction occurs, the potassium release could raise the potassium level of the blood stream as high as 11 to 13 meq. per liter, which would probably have a direct effect on the heart, causing cardiac standstill and death. It is interesting in these experiments that the pig dies of hyperkalemia in this manner, but the dog does not. The reason is that the dog red cell does not contain potassium in the same relative quantity that the pig red cell does. Since the human red cell contains the same amount of potassium as the red cell of the pig, it seems reasonable to transfer this same mechanism of death to man. High values occasionally occur when patients are provided with inadequate quantities of fluids and electrolytes (tissue breakdown and oliguria).

Beloff and Peters,[6] in a series of papers, demonstrated the presence of a proteinase in the normal skin of man and animals. This proteinase was seen to disappear after the skin had been burned. They postulated that either the enzyme left the skin that was damaged and entered the circulation, or else an inhibitory substance entered the damaged tissues and destroyed the enzyme. The same authors subsequently demonstrated that the enzyme escaped into the circulation.[7] Zamecnik, Stephenson, and Cope[103] reported the appearance

of a peptidase which was found in the lymph return from the burned legs of dogs. They were able to identify this same enzyme in dog serum, muscle, skin, subcutaneous tissue, and erythrocytes, and also in blood and blister fluid from human burns. Menkin[61] described a polypeptide of low molecular weight which was capable of causing an increased capillary permeability and was present in inflammatory exudates of various types, which he called "leukotoxin." Cullumbine and Rydon[17] substantiated the existence of leukotoxin but pointed out that it probably does not exist in the circulation since it is rapidly destroyed on incubation with blood serum or plasma. However, these authors were interested in the local effects of leukotoxin and carried out a series of experiments with the material made from burned rabbit skin. Subcutaneous injection of this substance in normal animals produced local edema of the area, hemoconcentration and hyperglycemia, as well as many of the other changes which are usually seen following shock resulting from a burn. Further experimentation revealed that the local edema fluid, produced by the subcutaneous injection of leukotoxin after approximately 48 hours, produced a toxin which was similar to that described by Wilson.[101] Previous investigations by Stoner and Green[91] have shown that shock induced by various means, including dehydration from hypertonic glucose injection, caused an increase in the adenosine equivalent of the blood. Cullumbine[18] substantiated the work of Stoner and Green by demonstrating an increase in the adenosine equivalent of the blood following the burning of rabbits. In addition he extracted 30,000 to 60,000 units of leukotoxin from the burned area of rabbits and injected this subcutaneously into normal animals and showed an equal increase in adenosine equivalent of the blood, similar to that which was produced by burning.[19]

The foregoing experiments have again raised the question of the possible formation of a burn toxin. That the chemical substances discussed above are produced from burned areas has been well substantiated, but whether or not these materials are actually toxins or simple chemical breakdown products remains to be proved. Most of the experimental studies which propose the formation of a toxic substance as the cause of death have failed to eliminate fluid deficits and internal fluid shifts as a basic mechanism in the death of the organism. Cross-transfusion experiments have been carried out from time to time, some tending to show that toxins are evident and others apparently completely disproving this theory. Giraldi, Peterson, and Cole[39] carried out a series of cross-transfusion experiments in dogs that had been burned. To rule out the possibility that a burn toxin, if it is formed in the burned area, may be destroyed as it passes through the general circulation, these investigators made a direct connection between the burned area and the normal animal. This was done by connecting the vena cava, draining the burned area, in most cases the hind extremities of the dog, directly to the normal animal, and the return blood flow was permitted through an artery-to-vein connection in the neck of the normal and burned animal. A series of normal animals were connected by means of a similar cross-circulation, and it was found that there was an average drop of 19 ml. in the blood pressure and a mortality of 16 per cent in

these animals. When a burned dog was connected to a normal animal by means of cross-circulation, there was better than twofold increase in the drop of blood pressure averaging 42 ml., and an increase in mortality to 27 per cent. That these differences might be due to changes in blood volume and internal fluid shifts is not eliminated in this experiment.

At present, there is still little conclusive evidence of the presence of a toxic substance in burned patients. The possibility that such exists cannot be ruled out, and the search for a burn toxin should continue. Whether a burn toxin is ever found may be of little importance, but the ingenious experiments that have been devised by many of these investigators in their attempts to find a toxin have led to the discovery of many of the underlying basic fundamental chemical and enzymatic processes that occur following injury to tissue. Although we are unable to interpret many of these findings in light of our present knowledge, it is certain that many of the facts which have been revealed incident to the search for a burn toxin will eventually serve as fundamental building stones of the total picture of man's reaction to injury.

PATHOLOGIC CHANGES IN SPECIFIC INTERNAL ORGANS

The interpretation of the significance of the gross and microscopic changes of various tissues removed at autopsy in patients who have died from extensive cutaneous burns is extremely difficult. There can be little doubt that the changes seen are very often due to the form of treatment given or due to the lack of treatment. There is no evidence to indicate that any specific pathologic changes, except those occurring at the site of injury, are pathognomonic of burns. In this review, organs will be discussed as single entities, but it should be borne in mind that most of the changes seen are a reflection of that organ's participation in the total body response to injury.

Central Nervous System.—There have been no recent studies on the pathology of the central nervous system following thermal injury. The most common pathologic finding in the brain is the presence of moderate to severe edema. Gibson,[37] and Walker and Shenkin[94] both report edema, increased intracranial pressure, and herniation of the cerebellar tonsils through the foramen magnum. It would seem likely that these changes are secondary to treatment rather than a primary result of the thermal injury. There is increasing evidence to show that the water content of the uninjured cell increases because of the electrolyte shifts into the burned area. Fox,[34, 35] and Rosenthal and Tabor[78] have shown experimentally that sodium shifts into the burn wound in excess of water. Potassium shifts from the burn wound in amounts approximately equivalent to the sodium gained. The diminution of sodium and other constituents of the blood leads to a hypotonicity of the intravascular fluid with a resulting shift of water intracellularly. Such a shift of fluid and electrolytes can be greatly magnified if solutions containing inadequate amounts of electrolyte are administered. This can become so severe as to cause intense edema of the unburned tissues, including the brain, with resulting water intoxication.

The study of heat stroke by Malamud, Haymaker, and Custer[62] is of interest with regard to the effect of heat on the brain. In a survey of the

clinical and pathologic findings in 125 fatal cases of heat stroke they noted the presence of hemorrhage, edema, and cone pressure on the cerebellum. These findings did not correlate with the degree of hyperthermia but did correlate with the degree of shock and they concluded that they were probably secondary manifestations and not primary. Degenerative neuronal change was a constant feature of all of their cases and they postulated that these changes were of primary hyperthermic origin. These changes could be correlated with the duration of hyperthermia and could be traced through successive stages from acute and chronic cell alteration to disappearance of neurons and their replacement by glia. How much of this study can be applied to thermal injury is difficult to ascertain since the majority of burned patients are subjected to intense heat in a specific area of the body and for a brief period of time. Most burns probably do not raise the body temperature more than a degree in the early stages. That degenerative changes can occur from hyperthermia has been shown by these authors and it may be that in severe burns involving a large portion of the body surface this mechanism may play a role in the fatal outcome.

Primary Lung Injury.—Moritz, Henriques, and McLean[68] carried out a detailed study of the effects of inhaled heat on the respiratory passages and lungs. They demonstrated that extremely high heat, sufficient to cause instantaneous burning of the skin, was dissipated so rapidly that it had little or no effect upon the respiratory passages. This was dry heat of the type seen in conflagrations where large numbers of people are injured. They were able to show that the inhalation of 500 c.c. of air at 142° C. would be cooled to 38° C. as it passed through the respiratory passages and thus release only 13 calories of heat energy in the body. However, all of this heat loss could be rapidly neutralized by the evaporation of the water that would be required to saturate that amount of dry air in the passages. The final effect would be no change in temperature within the respiratory passage. If, on the other hand, the same amount of moist air at the same temperature were inhaled, the release of heat energy would be great enough to cause severe burning of the respiratory passages. (At any given temperature, moist air has more heat to release than does an equal volume of dry air.) They were also able to show that extreme degrees of heat (enough to burn the face instantaneously) could produce a rapidly fatal obstructive edema of the glottis without further respiratory tract injury. Thus, they showed that the inhalation of dry or moist hot air may destroy the upper tracheal mucosa without causing thermal injury to the lungs. A severe tracheitis may develop which predisposes to bronchopneumonia. When heat of sufficient intensity to cause injury reaches the pulmonary parenchyma, there are dilatation of large and small bronchi, hemorrhagic edema of the peribronchial connective tissue, and generalized hyperemia of the peripheral and central pulmonary parenchyma. These experiments clearly demonstrate the difficulty in producing a burn of the actual lung parenchyma. They point further to the fact that many fatalities, which are diagnosed as due to respiratory burns, are more frequently deaths due to pulmonary edema and asphyxia resulting from the inhalation of either smoke

or other fumes which have been produced by combustible materials. These findings were substantiated clinically following the Coconut Grove fire in Boston (Cope and Rhinelander[12]).

Secondary Lung Pathology.—That many burned patients die in the first seventy-two hours after injury from pulmonary edema has been noted in all pathologic studies of burned patients. The difficulty in producing a primary pulmonary burn, as pointed out by Moritz and co-workers, emphasizes the fact that most of these cases of pulmonary edema are secondary to the inhalation of noxious fumes or treatment. That large volumes of fluid are required to sustain a burned patient through the shock phase is based on an abundance of experimental and clinical evidence. That the circulation can be overloaded by such treatment, especially if large volumes of hypertonic solutions are used, must be kept in mind in order to prevent this severe complication. Eaton[26] studied the problem of pulmonary edema following a period of hypotension. He showed that following hypotension that had persisted for two hours as a result of removing 25 per cent of the blood volume in dogs, certain specific changes occurred: (1) a rise in pulmonary artery pressure and systemic venous pressure while systemic arterial pressure remains low; (2) a rise in the pulmonary moisture content concomitant with a drop in plasma proteins and a rise in hematocrit; (3) following this, a drop in pulmonary moisture while plasma proteins remain low and hematocrit high; (4) a later rise again in pulmonary moisture at which time the plasma protein concentration fell to the lowest level noted; (5) a gradual return to normal. He noted an aggravation of the pulmonary edema when the animal was treated with intravenous saline solution. In addition to the above, an increase in pulmonary transudation was substantiated by noting the finding of an increased pulmonary lymph flow. The histologic evidence showed pulmonary edema, congestion, and hemorrhage to have occurred as early as ten minutes after the blood loss and to have persisted up to five days. The important point of this work is that following a period of hypotension (of sufficient length and severity) pulmonary edema occurs which can then be aggravated by treatment with salt solution, plasma, or blood. Prevention of such an occurrence by early and adequate therapy offers the only satisfactory method of management. Eaton further suggests that the pulmonary transudate, with its high protein content, may be an excellent culture media for implantation of organisms from the nose and mouth.

Kidney.—There is no investigative work to suggest that thermal injury has any direct effect upon the kidney, but there is good evidence to indicate that acute tubular necrosis leading to acute renal insufficiency is a common sequela to prolonged shock which often accompanies a burn. Gibson[37] reported autopsy findings from 6 patients with extensive burns, all of whom showed acute tubular degeneration in the proximal and distal convoluted tubules, accompanied by hyalin or pigmented casts of red-brick or yellow-brown color. Goodpastor[40] reported the autopsy findings of 47 patients who died of extensive burns, and, of these, 20 patients had morphological changes in the kidneys. All of the patients with kidney changes were in the group of extensive burns where the existence

of shock for prolonged periods of time was known to have occurred. In addition, these patients had evidence of gross hemoglobinemia and hemoglobinuria, and most of them showed pigmented casts and tubular necrosis. Lucke[55] studied the pathologic material available at the Army Institute of Pathology from patients who died in World War II. He noted a characteristic set of morphological changes in the kidneys of patients dying from all types of shock, including burns, blackwater fever, hemolytic transfusion reactions, and many other conditions which would lead to severe or prolonged hypotension. The changes seen were primarily in the renal tubules, varying from slight degeneration to complete necrosis. The lesions were focal and, if examined after the seventh day, beginning regeneration was often noted. Pigmented heme casts and nonpigmented hyalin casts were often seen in the tubules. He termed this picture "lower nephron nephrosis," because he believed the distal tubule was the portion of the nephron most frequently involved. Martineau and Hartman[59] reported the pathologic study of the kidneys of 84 experimentally burned dogs and of 20 patients who had died of severe burns. They described four major changes: (1) degenerative changes in the tubules, (2) congestion of the capillaries and venules, (3) tubular casts, and (4) lesions due to infection. They concluded that this altered morphology is due to two principal causes: shock and intravascular hemolysis. Prolonged shock causes irreversible tubular degeneration, and this is further complicated by the formation of casts due to hemoglobin in the urine. Yuile, Gold, and Hinds[102] have shown, by experimental studies, that the products of hemoglobin in the renal tubules are of secondary importance since the kidney is first damaged by prolonged shock or toxins of various types. Acute tubular necrosis may develop, and hemaglobinemia may be more likely to cause the formation of granular casts. Excellent reviews of the renal lesion which accompanies prolonged shock with or without myoglobinuria or hemoglobinuria are available (Bywaters and Beall,[9] Maegraith, Havard, and Parsons,[57] Corcoran and Page,[15, 16] Lucke,[55] Mallory,[58] Moon,[63] Van Slyke,[93] Smith,[87] and Oliver[70]). These studies demonstrate that the anatomic changes seen in the kidneys after burns are identical with those seen following ischemia, and it is generally accepted that the existence of intravascular hemolysis or the liberation of myoglobin from crushed tissue will precipitate out in the renal tubule when aciduria exists and may exaggerate an already precarious situation. In 1948, Dziemian[25] performed renal function studies in goats in whom third-degree burns involving 50 per cent of the body surface area had been produced. He noted that the glomerular filtration rate remained relatively constant, but that there was some increase in the filtration fraction due to a fall in renal plasma flow. Haynes, DeBakey, and Denman[48] carried out 16 renal clearance studies on 8 severely burned patients with 15 to 80 per cent of the surface area involved. All of these patients were adequately treated by present-day standards, and they noted an increased glomerular filtration rate, a normal effective renal plasma flow, and an increased filtration fraction. These changes occurred within the first 48 hours after injury and returned toward normal after 2½ to 3 weeks. These authors also studied tubular function and found that the maximum tubular capacity was within

normal limits in severely burned patients who received adequate treatment. There was indication in one patient of an increasing excretory capacity of the tubules three weeks post burn. The cause of these changes remains unknown, but the authors suggested that (1) overhydration, (2) hyperadrenalism, (3) pyrogenic response, (4) hypoproteinemia, (5) increased adrenaline secretion, or (6) a thyroxin increase could possibly account for them. Cope,[13] in a study of thyroid function in patients after thermal injury, found no increase in the protein-bound iodine. From this finding it is not likely that there is any increase in thyroxin output following thermal injury.

Liver.—In 1899, Bardeen[4] stated that primary hepatic necrosis occurs following thermal injury. In fact, the degree of injury is often proportional to the severity of the burn. Wells[98] first demonstrated that tannic acid used in the treatment of the local burn wound was toxic to the liver and suggested that the liver necrosis seen after burns was due to this agent. That tannic acid can increase the liver damage has been shown by Walker and associates,[95] and Hartman and Romence.[45]

Hartman and Romence,[45] Baker,[3] and Gillman and Gillman[38] have shown that liver damage may occur in burns not treated with tannic acid or other escharotic agents. That some necrosis of the central zone of the liver occurred, as well as fat infiltration, and impairment in liver function was thus established. However, none of these workers believed that the histopathologic changes seen were sufficient to account for the death of the patient.

Clark and Rossiter[11] suggested that the changes seen in experiments with rabbit liver slices were probably due to the circulatory changes following the burn rather than the thermal injury as such. There is no recent evidence to indicate that liver damage which occurs is not secondary to shock or an altered metabolic state.

That some degree of functional hepatic impairment does exist has been demonstrated by several workers. Walker and co-workers[95] studied hepatic function in 154 burned patients. They employed the van den Bergh test because they believed it reflected the over-all liver function best, and because most of the earlier patients that had received tannic acid therapy had had this test performed. Ninety-three per cent of the patients treated with tannic acid showed an abnormally high serum bilirubin, while only 53 per cent of the group treated with pressure dressings showed a similar response. Recently, James and co-workers[54] in studying the anemia which follows thermal injury, undertook the study of liver function. Their studies showed the most constant changes to be an increase in the urine urobilinogen excretion, and alterations in the albumin-globulin ratio. Of the 15 patients studied, 6 died, and necropsy in 5 did not reveal any constant pathologic changes in the liver, but there was evidence of fat infiltration, increased amounts of pigment in the reticuloendothelial cells, focal necrosis, and congestion in the liver substance.

Shock, with reduced hepatic blood flow and subsequent anoxia, usually causes some functional impairment of the liver. Recent reviews by Wilhelmi,[100] Wiggers,[99] Zweifach,[104] and Engel[28] have discussed these changes and they may be summarized as follows: the glycogen stores of the liver become depleted

and nitrogen metabolism is markedly altered. The capacity of the liver to synthesize glycogen is decreased, and its ability to deaminize amino acids is impaired. The energy reserves represented by stores of adenosine triphosphate (ATP) and adenosine diphosphate (ADP) are diminished and nitrogenous metabolites accumulate intracellularly. There is also a rise in blood amino nitrogen. Engel[29] has shown a good correlation between the fall in portal blood oxygen content and the rise in blood amino nitrogen. He also found a correlation between the fall in blood pressure and the rise in the amino nitrogen of the blood in animals.

It is also well known that certain changes in the liver occur as a response to injury in patients or animals not in shock. These include the tendency to fatty metamorphosis of the liver, abnormal carbohydrate metabolism, and the development of ketosis.

All of the above changes are included merely to show that many of the functional changes in the liver may be a part of man's response to injury, or secondary to shock with an impaired hepatic blood flow. That primary liver injury may occur in severe thermal burns cannot be denied, but with the evidence at hand the likelihood of these changes being of a secondary nature seems most probable.

Adrenals.—Weiskotten,[97] in a study of the pathologic anatomy of burned patients, concluded that the most marked and specific changes occurred in the adrenal glands. In 1946 Selye,[83] in his description of the general adaptation syndrome, described similar changes in the adrenals following a variety of stressful situations. The glands increased in weight from a normal of 4-7 Gm. to 20-25 Gm. The enlargement occurred in the adrenal cortex with the individual cells undergoing hypertrophy associated with a loss of their lipid granules. Harkins[44] has shown that the cortical lipoid which is lost is predominantly cholesterol. The ascorbic acid content of the cortical cells is rapidly diminished. All of these changes are reversible if the subject recovers (Sayers[80]).

Selye[84] has also shown that the adrenal medulla undergoes a change with the discharge of the chromaffin granules and vacuolization of the cells.

These morphologic changes in the adrenal gland begin almost immediately and reach a peak at about 48 hours after injury. Of great importance in the treatment of the burned patient is the knowledge of these morphologic changes in the adrenal gland and what they mean. These changes, accompanied by an increased output of adrenal hormones, are a part of the normal response to stress. There is very little evidence that even in severe stress, such as a thermal burn, adrenal exhaustion or insufficiency is likely to develop. Thus, there is no reason to believe that additional exogenous adrenocorticotropic or adrenal hormones should be administered (Cope[14]).

Gastrointestinal Tract.—Curling[20] first called attention to ulcers of the gastrointestinal tract following burns. Harkins,[44] in a review of the literature, found 107 cases of ulceration following burns and in 1942 added 10 cases to his original series. Weigel and co-workers[96] reviewed the literature from 1942 to 1952 and found 17 additional cases and added 7 cases of their own.

Acute ulcerations following a burn may be found anywhere in the gastrointestinal tract, but have been reported by Selye,[83] Hartman,[46] Prosinger,[75] and Weigel,[96] to occur most frequently in the stomach and duodenum.

The ulcers vary in size and depth from pinpoint superficial hemorrhagic areas in the mucosa to large (3 to 4 cm.) punched-out areas eroding deep into the muscularis and in some cases perforating. The margins of the ulcers are not thickened or everted and the base is usually smooth, glistening, and grayish red. Microscopically there is little or no cellular reaction (Hartman,[47] Davis,[21] and Weigel[96]).

The etiology of these ulcers has been a subject of considerable controversy for many years. Moynihan[69] believed they were of a toxic nature and therefore similar to those seen in septicemia and uremia.

Hartman[46, 47] produced gastrointestinal ulcers in dogs with third-degree burns involving 50 to 60 per cent of the body surface area. He noted marked hyperemia and edema of the mucosa and suggested this as a precursor to ulcer formation. It was his conclusion that infection was the major cause since gastrointestinal ulceration was ten times more frequent in a group of dogs with a high instance of wound infection as compared to a group of animals with a similar burn in whom infection was controlled by antibiotics. He was able to reduce the incidence from 77 per cent in the control group to 23 per cent in the penicillin-treated group of dogs. Freisen[36] studied acute ulcers in both rabbits and dogs which had been burned. He noted the following series of events: there was a loss of plasma into the burn wound with a resultant hemoconcentration; this was followed by stasis and increased viscosity of the blood, which led to extreme mucosal congestion; the resultant stagnant anoxia caused extravasation and superficial necrosis and made the mucosa far more susceptible to the eroding action of gastric juice. He concluded, therefore, that hemoconcentration was the most important single factor in the genesis of ulceration. Further support was gained when none of the animals that did not develop hemoconcentration formed an ulcer.

The difficulty with accepting either of these theories is the demonstration by Selye[83] that similar ulcers occur from intense emotional stress (air-raid ulcers) and from a wide variety of other stressful situations that are not accompanied by infection or hemoconcentration.

On the other hand, it has been shown by Gray and associates[41] that increases in circulating adrenaline and/or corticosteroids cause an increased secretion of hydrochloric acid by the stomach. It may be that the congested mucosa is more susceptible to the increased acid production, and, therefore, any set of circumstances in which congestion of the mucosal vessels occurs concomitantly with increased adrenal activity (stress) may predispose to ulcer formation.

Thyroid.—There are no anatomical changes in the thyroid gland which are specifically related to thermal injury. Histologic evidence of increased thyroid activity has been noted after burns, as well as an increase in the total weight of the gland. Uotila and Pekkarinen[92] and Rumiantsev[79] noted increased

thyroid activity following burns in rabbits. Sellers and associates[81, 82] studied both the adrenal and thyroid under several types of stress. There was no increase in the urinary nitrogen excretion of thyroid-fed rats as compared to the control animals, although a reduction in the amount of nitrogen in the urine was observed when the rats were thyroidectomized as compared to the amount secreted by a control group.

Cope and co-workers[13] studied the metabolic rate and thyroid function in burned patients. Thyroid function was studied by means of determining the protein-bound iodine of the serum and the rate of uptake of I^{131} by the thyroid gland. Although the metabolic rates were increased in these patients as much as plus 30 to plus 60 per cent, the protein-bound iodine and the I^{131} uptake were within normal limits. They concluded that the elevated metabolic rate may account for some of the wasting which occurs in severely burned individuals but that the thyroid is not the cause of the increased metabolic rate.

Thymus.—Involution of the thymus occurs with any major stress, but there are no anatomic changes specifically related to thermal injury (Selye[83]). It has been established that the adrenal gland in some way mediates this involution, since adrenalectomized animals fail to show this response (Dougherty and White[23]). Further evidence was added by Soffer[88] when he demonstrated the shrinkage of a thymic tumor following the administration of ACTH. He has since added 4 additional cases to the original (Soffer[89]). Davis and associates[22] have recently reported the case of a 3-week-old child with an enlarged thymus which spontaneously disappeared following a burn involving 20 per cent of the body surface. Roentgenograms taken four hours before injury show an enlarged thymus, and repeat roentgenograms, fifteen hours post burn, show an almost complete disappearance of the thymus.

The changes which do occur as a result of stress are a loss of weight of the gland, preceded by nuclear pyknosis with complete dissolution of the thymocytes. Large macrophages engulf the dead cells and remove them via the lymphatics, and the thymic reticulum reverts to its original epithelial type. Ingle[53] believes the involution of the thymus is a more sensitive indication of ACTH activity than the hypertrophy of the adrenal. The involution of the thymus which follows a burn is probably the result of adrenal hyperactivity which occurs following nonspecific stress.

Spleen and Lymph Nodes.—Weiskotten[97] described rather prominent changes in the spleen and lymph nodes of severely burned patients. He noted edema and necrosis of the germinal centers of the lymph follicles. Phagocytes appeared to ingest the dead cells and the process often continued until the follicle was represented by a central area filled with phagocytes and a surrounding ring of lymphocytes.

The same changes were seen in the lymph nodes as were seen in the follicles of the spleen. Nodes from all parts of the body were studied and the author concluded that because of this universal effect on lymphoid tissue a circulating factor must be responsible rather than a local factor or one carried via the lymphatics per se.

Similar changes had been described by McCrae[60] and Bardeen.[5] Flexner[32] had suggested that the anatomic arrangement of the central artery in the lymph follicle was the cause for the central necrosis which occurred. He believed the cause to be a circulating toxin. McCrae[60] noted that the changes were identical to those which were seen following typhoid fever and other acute infections.

Folgia and Selye[33] described the same changes during the alarm reaction. They included the reaction in the thymus, as described previously, as a part of the over-all reaction of the lymphoid system to stress. The reaction in the lymph nodes and spleen was not as great as that in the thymus and it was not as completely prevented by adrenalectomy.

Dougherty and White[23] have shown a marked lymphocytosis following the injection of ACTH in rats. They have also demonstrated that the total mass of lymphoid tissue varies inversely with the activity of the adrenal cortex (Dougherty and White[24]). Pearson, Eliel, and Rawson[73] reported the results of study in 6 patients with lymphomatous tumors who were treated by ACTH. All patients showed a dramatic response to therapy, manifested by a decrease in the size of the lymph nodes and spleen. Histologic studies of a lymph node from one of these patients revealed a disappearance of the germinal centers and a decrease in the cellularity.

The evidence seems to indicate that the changes seen in the lymphoid tissue of the body, following a thermal burn, are not specific for this type of injury but are a part of the pituitary-adrenal response to stress.

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Surgical History

CONDUCTED BY JOHN R. PAINE, M.D.

THE STORY OF THE DEVELOPMENT OF SURGERY FOR THE PATENT DUCTUS ARTERIOSUS

RICHARD H. MEADE, M.D.
GRAND RAPIDS, MICH.

OF ALL the congenital defects of the cardiovascular system none can be more perfectly corrected than the patent ductus arteriosus. In every case in which there is patency of this structure, restoration to normal can be produced by division or ligation of it, if there is not too extensive endarteritis, or marked hypertrophy of the heart. This operation is now being performed throughout the world with practically no mortality. Although ligation of the ductus was first seriously suggested in 1907 the operation was not successfully completed until 1939.

It has been known for a great many years that the ductus arteriosus plays an important role in the circulation of the fetus, and that it remains patent for several days after birth in most instances. Its persistent patency does not interfere with normal circulation until some years have passed, and the effect of the arteriovenous fistula is shown in the enlarged heart. Furthermore, it has been shown, notably by Maude Abbott,[1] that endocarditis develops in more than a fourth of the patients if they live to puberty. In her series of 92 cases of patent ductus followed for many years, 21 of the patients died from endocarditis. Thus, although in the early years there may be no trouble, as the patient grows older symptoms will appear. These facts were known to John Munro[11] of Boston in 1907, and he believed that the ductus could be ligated with impunity. He was a surgeon of great experience and well qualified to undertake a new operation. On May 6, 1907, he addressed the Philadelphia Academy of Surgery on the subject, "Ligation of the Patent Ductus Arteriosus." He said: "That I may be allowed to bring this suggestion for a new operation before your Society, I ask on the basis that it has not been hastily conceived. On the contrary, long ago I demonstrated its technical possibility on the cadaver of new born children, and felt that it was justifiable on the living. At various time I have tried to inspire the pediatric specialist with my views, but in vain. Now, in view of the recent advances in cardiac surgery, for much of which we are indebted to the surgeons of this city, I will venture to place my ideas before you, asking that you do not dismiss them hastily." He then went on to record the case of a girl baby that pre-

sented evidence of heart disease and died after several weeks without any real cyanosis. At autopsy the only abnormality was an open ductus arteriosus "lying easily within reach behind the sternum. The simplicity of the remedy was so striking that I at once made further dissections, and satisfied myself that it would be possible to ligate the duct provided a diagnosis could be made beforehand. In regard to making a diagnosis however, my pediatric advisors were not reassuring." He then spoke of studies made on the ductus, and the effort to recognize distinctive heart sounds. As the ductus is normally open during the first few days of life, it was thought that it would be possible to establish the auscultatory signs that were typical from examination of many newborns. This did not prove to be true, although Townsend examined 100 newborns during the first three days of life. This discussion seems strange to us today as one usually considers the murmur heard in patients with patent ductus as being easily recognized because of its loud and continuous sound, and of being diagnostic. Munro then discussed the question of the etiology of the delay in closure of the ductus and said nothing was known about this.

His description of the characteristic findings in a case of patent ductus is still true in most respects. First, he said, that there was no cyanosis, except occasionally in late life. "Cardiac dullness is increased laterally, and there may be projection and pulsation of the dullness upwards in the upper intercostal spaces. This projection is visible by x-rays. A loud systolic whir conducted into the cervical vessels may be heard, but as a matter of fact there are no definite auscultatory signs established as yet." Of the 26 cases collected recently, half lived to puberty. Death, he said, follows from atelectasis, general edema, pleural exudate, pneumonia, endocarditis, etc.

Munro then went on to say: "Why should we consider surgical interference in cases of open ductus arteriosus? Because in spite of the fact that some cases may live to puberty the chances of which must be small, we have the cardiovalvular lesion which is, relatively speaking, superficial. Furthermore the anomalous vessel is of good size, its ligation must be followed by instant and permanent restoration to a normal function of the lungs and arteries, and it can be reached by a short surgical route."

He then described the operative approach in these words: "The operation I would propose, as demonstrated on the cadaver, is as follows. Under ether anesthesia, which I prefer to chloroform in any case involving collapse of the lung, the sternum can be easily split along its center or a little to the right, opposite the second costal cartilage. This is easily done with a knife. The sternal halves are then retracted, ample room for working being obtained. The right pleural cavity will probably be opened but the left one will not. Judging from analogous cases in surgery, this should not be serious, but if necessary the physiologist's apparatus for maintaining artificial respiration could be employed. I hardly believe that it would be needed. After retracting the thymus upward, the pericardium is exposed. Its reflection lies so high on the great vessels that the ductus to all intents and purposes is intrapericardial. In the upper angle the aorta will be seen on the patient's right

and the pulmonary artery on the left. By following close to the aorta toward the undersurface of the arch the ductus, as large as the aorta itself, will be seen as the first vessel to the left pointing upward and a little to the right. Both pulmonary branches lie too far posteriorly to be seen, and by keeping close to the aorta the main pulmonary trunk will escape injury. On pushing through the tissues with blunt dissection the ductus, theoretically, should easily be surrounded with a ligature. It is a question whether or not simply crushing it would not accomplish as much, and in case of necessity, I believe that it would be worth trying. After closing the pericardial wound the sternum can be sutured or not and the skin closed."

As the diagnosis was not considered to be easily made at that time, he wondered if one would be justified in operating when the diagnosis was not established. Speaking of this he said, "Would it be justifiable to subject a child to this risk without knowledge of the exact lesion? In a case with beginning atelectasis or other evidence of impending death from circulatory disturbances, with a reasonable basis for believing that the duct were open, it seems as though such an operation would be justifiable. I doubt if it would materially hasten a fatal issue in case the diagnosis were not confirmed."

Why was it then that this operation was not attempted at that time? Munro himself was a well-known surgeon with great experience, and surgery had advanced to a stage not far behind our techniques of today. For instance, in abdominal surgery, W. J. Mayo[9] had published a review of 1,500 operations on the gall bladder and bile passages with a mortality of only 4.43 per cent. The last 272 cases of cholecystectomy had been done with a mortality of 1.4 per cent. Thyroid surgery was being done as shown by C. H. Mayo's report[8] on 110 cases of thyroidectomy for Graves's disease with 9 deaths, and with only 2 in the last 64 cases. This report is especially interesting in view of the fact that only five years before, in an article in the *Lancet*,[12] the professor of comparative pathology in the University of Durham had said that no definite treatment for exophthalmic goiter existed, and did not mention the possibility of surgery. Thoracic surgery at this time was confined to suture of stab wounds of heart in rare cases, drainage of empyema and lung abscess, and the removal of chest wall tumors. Operations in the open chest were not successful in spite of Munro's remark about the use of the physiologist's apparatus for maintaining artificial respiration. Another important deficiency of the day was the lack of blood transfusions. It is true that in this year (1907) Crile[2] reported on his experience with blood transfusion using artery vein anastomosis in 14 cases. Landsteiner,[6] in 1900, had discovered the presence of isoagglutinating and isoagglutinable substances in human blood, and the next year[7] had divided blood into three groups on the basis of their agglutinating reactions and had indicated their practical significance. In spite of this work Crile believed that blood could be safely transfused from any one member of the same species to any other member. In his own experience he had no reactions, but he had limited the procedure to only the gravest and apparently hopeless cases. So, in spite of surgery having developed to a high

degree in general, thoracic surgery was still in its infancy, and blood transfusion was not available. It is indeed fortunate that no one at that time undertook to carry out the operation described by Munro.

Thirty years after John Munro had suggested ligation of the patent ductus, it was finally attempted by John Strieder[15] in Boston. Following Munro's presentation no pediatrician had been willing to refer a patient for operation, and the years had gone by without further interest in the subject. Indeed, Maude Abbott,[1] the greatest authority on congenital heart disease, had written in one of her last articles that although Munro had suggested ligation of the patent ductus she knew of no attempt having been made to do it, and she felt that this was most fortunate as she was sure it would be followed by endarteritis, and the end condition would be worse than the original one. This view must have been shared by many, but one among them did not agree, and he was Ashton Graybiel of the Massachusetts Memorial Hospital. He felt that the operation was a good one and interested John Strieder in the subject. Dissections were carried out on cadavers, and with the cooperation of John Munro's son, Donald Munro, a search was made through his papers to see if he had ever attempted the operation. No such record could be found, and nothing had been published in the literature on the subject. Reginald Fitz referred to Strieder a patient with a patent ductus complicated by severe bacterial endocarditis. It was hoped, contrary to the opinion of Maude Abbott, that ligation of the ductus would control the endocarditis and cure her. The operation was done on March 6, 1937, but it was found that the aorta and pulmonary artery were so intimately adherent that they could not be separated posteriorly. Hoping to achieve some good the ductus was sutured, and the thrill somewhat diminished. Following the operation she was in good condition for three days, and no murmur could be heard, but, on the fourth day, she developed acute gastric dilatation and died in spite of treatment. At the autopsy vegetations could be seen to extend from the ductus down to the pulmonary valves. At the meeting of the American Association for Thoracic Surgery on June 1, Strieder[15] presented this case report in the discussion period following Blalock's paper on tuberculous pericarditis. Although a number of the pioneer cardiac surgeons of the world were present, no one was sufficiently impressed by Strieder's report to remark on it. In presenting his case Strieder had this to say, "We are reporting this in some detail later, but I thought that I might take the opportunity to present it to the Society in case anyone had thought along similar lines and would be interested in trying it as a prophylactic measure in youngsters before they already had dilatation and hypertrophy of the heart, and also because 25 per cent of these patients with congenital heart defects die of subacute bacterial endocarditis or endarteritis." Almost a year later Graybiel, Strieder, and Boyer[3] reported the case in the *American Heart Journal*. In the conclusion of this article Strieder said that in the future in addition to ligating the ductus he would attempt to obliterate the adjacent portion of the pulmonary artery, so as to remove all the vegetations from direct contact with the blood stream,

and to allow the natural defenses of the body to kill the bacteria. He also said that the vegetations might be removed by a modified Trendelenburg operation.

Fifteen months after Strieder reported his attempt to ligate the ductus, Robert Gross[4] of Boston succeeded in doing so. His patient was a child with no complicating endarteritis or endocarditis. The news of this operation spread throughout the world. When Gross did his operation he was unaware of Strieder's attempt to do so. He had not been present at the meeting in Saranac Lake and did not at that time know Strieder personally. John Hubbard was head of the Congenital Heart Clinic at the Children's Hospital at that time and he was interested in getting someone to correct surgically some of the defects which he saw. He talked the matter over with Gross, and together they decided to attack the patent ductus first. They were familiar with Munro's article. Gross worked in the Harvard Medical Laboratory and perfected an approach to the ductus. His successful operation thus followed careful preliminary work, and he was fortunate in having a good patient on whom to operate.

The story of the attack on the patent ductus does not end with Gross's first case. Although Strieder spoke of the operation as being a good one to combat existing endarteritis, and to prevent its development, it was not until four years later that Touroff[16] of New York was able to demonstrate the truth of the hypothesis. He operated on a patient with a patent ductus, and with bacterial endocarditis, as shown by persistently positive blood cultures for *Streptococcus viridans.* As a result of the ligation of the ductus, all evidence of that defect and of the endocarditis disappeared. Following this demonstration this result became commonplace. The next step in the development of surgery for the patent ductus was again taken by Gross.[5] Not being satisfied with simple ligation of the ductus, as everyone knew division of a vessel was better than simple ligation, he began dividing his ducti. He modified some hemostats in such a way that he could apply them to the ductus, divide the structure, and then suture the divided ends, with healing. Everyone at once admitted that this was an important forward step, but the risk of the procedure seemed formidable; then Willis Potts[13, 14] made his important contribution. While watching a plastic surgeon one day cut skin grafts, after first stretching the skin with special skin-holding instruments, he suddenly thought that the same principle could be applied to hemostats so that they might firmly hold vessels without traumatizing them. He then went to see Mr. Richter, the man who had perfected his clamp for holding the aorta in his aortic pulmonary anastomosis operation for the tetralogy of Fallot, and asked him to make the homostat he had in mind. Mr. Richter got the idea at once and proceeded to make the instrument. It was perfect. Each blade had fine teeth that intermeshed with fine teeth on the opposite blade, and when the vessel was clamped with this it was securely held without damaging the intima. As copies of this instrument came on the market more and more surgeons began dividing the patent ductus.

It is interesting to remember what a debt surgeons owe the pediatricians and cardiologists for leading the way in the attack on this congenital heart defect. And also we must give credit to an instrument maker for his part in perfecting the operation.

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Book Reviews

La Valvola Mitrale. By Michele A. Chiechi and Charles P. Bailey. Pp. 561. Rome, Italy, 1954, "Il Pensiero Scientifico," Publisher.

This Italian monograph deals mainly with surgery of mitral stenosis. The authors' experience is based on the clinical material represented by 1,200 cases operated on at the Bailey Thoracic Clinic in Philadelphia.

All chapters are well elaborated. The description of the morphology and anatomical variations of the mitral valve, and certain concepts of the physiopathology of mitral disease are original contributions of the senior author. The operative indications and contraindications, the surgical technique, and the results of mitral commissurotomy do not differ fundamentally from those already established and described in previous works by C. P. Bailey.

This book is well written and is presented in an orderly fashion; it contains good illustrative and bibliographic material. It is to be recommended to those interested in the subject.

—Mansur Taufic

Roentgenologische Differentialdiagnose der Knochenerkrankungen. (The roentgenologic differential diagnosis of bone disease). By Hans Hellner and Hanno Poppe. An atlas of 903 pages with 518 figures containing 842 individual reproductions. Published by Georg Thieme Verlag, Stuttgart, Germany, 1956. Price DM 270.

This is one of the largest collections of radiographs of bone disease ever published. The reproduction of radiographs is faultless. Only infinite care for detail could have produced illustrations that have the quality approaching the actual viewing of the original films. Some of the reproductions are actually enlargements from the original, yet the blowing up has been achieved without sacrificing sharpness. The printing of radiographs as negatives (with only a handful of exceptions) is a welcome deviation from what has become customary in European publications. The work is a result of a review of over 75,000 films. It is based on films of 500 patients. Two features recommend this work above most other similar collections: (1) The authors have tried to publish atypical manifestations of bone diseases along with their more familiar appearance. (2) They have made an attempt to present early cases, especially in the tumor chapter, emphasizing the value of early diagnosis.

The omission of some more recently described entities such as aneurysmal bone cyst and infantile cortical hyperostosis is strange in such a detailed work. The American reader may find it unusual to find fibrous dysplasia listed as osteofibrosis deformans juvenilis-Uehlinger. This, however, is more than compensated by the wealth of cases of this condition. The stress on hyperparathyroidism (osteodystrophia generalizata-Recklinghausen) which is given extensive coverage, much more than other conditions, is surprising to a reader in this country. The atlas is organized by topographic region rather than by disease, which makes comparative study easier. These regions are narrowed enough so that many conditions occurring in the same location can be shown side by side.

The atlas is followed by a short and succinct discussion of differential diagnosis, which manages to compress considerable information into 77 pages of text. The organiza-

tion may be somewhat unorthodox, as, for instance, lumping into the same chapter osteopetrosis, generalized periosteal hyperostosis, with toxic osteoscleroses and osteoblastic metastases. Part III consists of 29 schematic skeleton charts indicating the preferred and frequently encountered localization of 29 common bone diseases. The separation of locations of skeletal tuberculosis as found in children and adults is an indication of the care for detail that permeates this whole book. This may have been carried to unnecessary extremes in the sketches of enchondromas dividing them into five different forms. (Example: Acroform, radiating, oligotopic, unilateral, total.) Part IV is named "encyclopaedia." It is a successful attempt to present in brief, dictionary form the definition and synonyms of the conditions covered. The fact that this part is only rarely dogmatic and yet manages to be fairly complete is a measure of its success.

—Alexander R. Margulis

Cardiac Diagnosis. By R. F. Rushmer. Pp. 447. Philadelphia, 1955, W. B. Saunders Co.

This book, together with other recent books such as *The Lung*, by Comroe et al., and *Pathologic Physiology*, edited by Sodeman, indicates the increasing usefulness of approaching clinical subjects from the physiologic viewpoint. Its general plan is to go from the normal physiology of the cardiovascular system to the abnormal. Methods of cardiac diagnosis are then presented, followed by a discussion of cardiac diagnosis itself. The strength of the book resides in the writer's clear writing style and the extensive use of schematic drawings for illustrating concepts. Conciseness is gained at the expense of omitting contrary viewpoints on certain subjects. Since the author does this deliberately, it indicates that it was not intended as a critical analysis but rather as a pedagogical work. Keeping this in mind, I think the book is excellent and it will no doubt be widely used by medical students and physicians.

—John A. Johnson

Correlative Neurosurgery. By E. A. Kahn, R. C. Bassett, R. C. Schneider and E. C. Crosby. Pp. 413. Springfield, Ill., 1954, Charles C Thomas. $19.50.

This is a factual account of teaching, investigation, and practice of neurosurgery and allied fields at the University of Michigan, written by a number of contributors all of whom with one exception are now on the Staff of the University of Michigan or have been on that Staff. It is quite extensively documented by references to the contributions of other authors.

It does not cover the entire field of neurosurgery but does include discussion of the following: skull x-ray, electroencephalography, radioactive isotope localization of brain tumors, the more common types of brain tumor, brain abscess, vascular lesions of the brain and spinal cord, prefrontal lobotomy, aphasia and apraxia, endocrinology in neurosurgery, tumors of the spinal cord, surgery of pain, craniocerebral trauma, closure of scalp defects, spinal cord trauma, and developmental anomalies.

Apparently the title "Correlative Neurosurgery" was chosen to indicate that it contains correlation of neurosurgery and neuroanatomy. In some of the chapters on brain tumors written by Kahn and Crosby, there is such a correlation with neuroanatomy. This is very well done and indicates that the neuroanatomist has developed real interest and understanding of the clinical aspect of these lesions.

The publisher has contributed much to the excellence of this book. The pages are large, and numerous photographs are correspondingly large and clear. Some of them occupy one-half of these large pages.

This is one of the best treatises written on neurosurgery. Neurosurgeons will find it interesting and instructive, but it should be especially valuable to the young neurosurgeon or resident in neurosurgery who will find much detail about some operative procedures. The medical student or general practitioner will probably not find a book on neurosurgery that will give them as much useful information with as little effort.

—William T. Peyton

The Relief of Symptoms. By W. Modell. Pp. 450. Philadelphia, 1955, W. B. Saunders Co.

The author of this book has devoted himself to the proposition that symptoms of disease per se are worthy of serious consideration. One hundred years ago this attitude would have been so common as to be trivial, but, as he points out, with the rapid advances in those parts of medicine which deal with diagnosis and cure, symptoms have been more and more overlooked. Moreover, any person dealing too seriously with symptoms is running the risk of being attacked as antiscientific and tending toward quackery. To justify his feeling that symptom relief is worthy of earnest attention, he indicates that the patients' feelings are as primitive now as they ever were and there is no moral reason and very few intellectual reasons for refusing to relieve the patients' symptoms. In addition, it is emphasized that some of the symptoms developed coincident with the progress of a disease are not always instantaneously reversed by abolition of the inciting factor and are therefore worthy of consideration in their own right as active contributors to the diseased state.

The first part of the book, which the author labels "Theory," deals with his justification for emphasizing the importance of dealing adequately with symptoms, the nature of relief of symptoms, the difference between symptoms and complaints, and the considerations, including placebo action, which one has to keep in mind when using drugs to relieve symptoms. In addition, the danger of relieving some symptoms is pointed out.

The second part of the book, labeled "Practice," takes up individual symptoms in detail. His choice of symptoms, the author believes, will cover over 95 per cent of those which will come to the internists' attention. His discussion starts with a chapter on pain, which is treated in some detail. This is done for a variety of reasons, among which is his feeling that it is the best understood, the least tolerable, the most common, and the best symptom to use as a model for discussion. His treatment of the pain experience, following the approach of H. C. Wolff, is analytical.

Part three of the book is labeled "Counsel," and consists of just one chapter entitled "Cortisone and the Masking of Symptoms." Here the author returns to a subject he introduced earlier in the book, which is the danger of suppressing too many of the biologic responses to a disease process. In so doing, both the patient and the doctor lose completely the ability to follow the course of the disease. Cortisone is used as the prototype of the drugs which could be called generalized symptom relievers.

I consider this a valuable book, worthy of serious consideration. If, however, its objectives are realized, care must be taken not to spend so much time and effort on symptom relief that none is left for the diligent search for and eradication of the primary causes of disease.

—John A. Johnson

Die Hand des Kranken. By Dr. Max Burger. Pp. 445. München, 1955, J. F. Lehmanns Verlag.

This is a fascinating book on a special phase of clinical diagnosis. It deals with the diagnosis of diseases affecting the hand and particularly changes in the hand which reflect disease processes elsewhere in the body. The introductory section on the normal hand contains a great deal of information about the normal growth and function of the hand. There are many interesting sidelights of a historical nature dealing with palmistry and the individuality of fingerprints. In the section on the diseased hand, there are chapters on the congenital deformities of the hand, diseases of the musculoskeletal apparatus, infections of the hand, the hand in patients with respiratory disease and diseases of the circulatory system, the hand in metabolic and endocrine disorders, neurologic diseases as expressed in the hand, and, finally, the dermatologic conditions seen in the hand. The book contains many excellent illustrations and diagrams. The bibliography is especially complete. This book should be of interest to all physicians since it expresses one phase of the art of medicine in a very scientific fashion.

—Leonard F. Peltier

Calendar of Surgical Meetings

1956

THE AMERICAN ACADEMY OF NEUROLOGICAL SURGERY. *Annual Meeting,* Nov. 1-3, 1956, Camel Back Inn, Phoenix, Ariz. Secretary, Eben Alexander, Jr., M.D., Bowman Gray School of Medicine, Winston-Salem, N. C.

AMERICAN CANCER SOCIETY, INC. *Annual Meeting,* Scientific Session, Oct. 29 and 30, 1956, Park Sheraton Hotel, New York, N. Y.

AMERICAN MEDICAL ASSOCIATION. *Clinical Session,* Nov. 27-30, 1956, Civic Auditorium, Seattle, Wash. Secretary, Council on Scientific Assembly, A. M. A., 535 N. Dearborn St., Chicago 10, Ill.

LATIN AMERICAN CHAPTER OF INTERNATIONAL SOCIETY OF ANGIOLOGY. *Third Meeting,* Nov. 8-11, 1956, Havana, Cuba. President, Armando Núñez Núñez, Calle 25 No. 510, Vedado, Havana, Cuba.

SOUTHERN SURGICAL ASSOCIATION. *Annual Meeting,* Dec. 4-6, 1956, the Boca Raton Club and Hotel, Boca Raton, Fla. Secretary, George G. Finney, M.D., 2947 St. Paul St., Baltimore, Md.

1957

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY. *Annual Meeting,* May 4, 6, and 7, 1957, The Palmer House, Chicago, Ill. Deadline for papers, Dec. 15, 1956. Secretary, H. T. Langston, M.D., 1919 West Taylor St., Chicago 12, Ill.

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS. *Annual Meeting,* May 1, 2, and 3, 1957, The Homestead, Hot Springs, Va. Secretary, John A. Taylor, M.D., 2 East 54th Street, New York 22, N. Y.

AMERICAN COLLEGE OF SURGEONS. Southern California Chapter. *Annual Meeting,* Jan. 18, 19, and 20, 1957, Biltmore Hotel, Santa Barbara, Calif. Secretary-Treasurer, Max R. Gaspar, M.D., 211 Cherry Avenue, Long Beach 2, Calif.

AMERICAN GYNECOLOGICAL SOCIETY. *Annual Meeting,* May 27, 28, and 29, 1957, The Homestead, Hot Springs, Va. Secretary, Andrew A. Marchetti, M.D., Georgetown University Hospital, Washington 7, D. C.

AMERICAN MEDICAL ASSOCIATION. *Annual Meeting,* June 3-7, 1957, Coliseum, New York, N. Y. Deadline for papers, Dec. 15, 1956. *Clinical Meeting,* Dec. 3-6, 1957, Auditorium, Philadelphia, Pa. Deadline for papers, July 15, 1957. Secretary, American Medical Association, George F. Lull, M.D.; Secretary, Council on Scientific Assembly, Thomas G. Hull, M.D.; address of both, 535 North Dearborn Street, Chicago 10, Ill.

AMERICAN SURGICAL ASSOCIATION. *Annual Meeting,* May 8, 9, and 10, 1957, The Palmer House, Chicago, Ill. Secretary, R. K. Gilchrist, M.D., 59 East Madison Street, Chicago 3, Ill.

AMERICAN UROLOGICAL ASSOCIATION. *Annual Meeting,* May 6-9, 1957, William Penn Hotel, Pittsburgh, Pa. Deadline for papers, Jan. 1, 1957. Secretary, Samuel L. Raines, M.D., 188 S. Bellevue Blvd., Memphis, Tenn.

THE CENTRAL SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 21-23, 1957, The Drake Hotel, Chicago, Ill. Deadline for papers, Oct. 15, 1956. Secretary, Charles D. Branch, M.D., 102 North St., Peoria, Ill.

NEW ENGLAND SURGICAL SOCIETY. *Annual Meeting,* Oct. 4 and 5, 1957, Mount Washington Hotel, Burton Woods, N. H. Deadline for papers, June 1, 1957. Secretary, Richard Warren, M.D., Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Mass.

THE PACIFIC COAST SURGICAL ASSOCIATION. *Annual Meeting,* Feb. 4-6, 1957, El Mirador Hotel, Palm Springs, Calif. Secretary, Carleton Mathewson, Jr., M.D., Stanford University Hospital, San Francisco 15, Calif.

PAN-PACIFIC SURGICAL ASSOCIATION. *Annual Meeting,* Nov. 14-22, 1957, Honolulu, Hawaii. Director General, F. J. Pinkerton, M.D., Room 230, Young Building, Honolulu, Hawaii.

THE SOCIETY OF UNIVERSITY SURGEONS. *Annual Meeting,* Feb. 7-9, 1957, Columbus, Ohio. Secretary, James Hardy, M.D., Hospital of the University of Mississippi, Jackson, Miss.

THE SOCIETY FOR VASCULAR SURGERY. *Annual Meeting,* June 2, 1957, Hotel Biltmore, New York, N. Y. Secretary, Henry Swan, M.D., 4200 E. 9th Avenue, Denver, Colo.

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1. R.C. Gaard, *Minnesota Medicine, 38*:637, 1955. 2. F.F. Foldes, *et al., J.A.M.A., 160*:168, 1956. 3. V.K. Stoelting and M.L. Hicks, *Canad. Anaes. Soc. J., 3*:107, 1956. 4. S.C. Cullen and C.C. Santos, *Anesthesiology, 16*:674, 1955.

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